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E. L. McBride M. D. C. M.
Prof. Pathology

MANUAL

OF

PATHOLOGY

INCLUDING BACTERIOLOGY, THE TECHNIC OF POSTMORTEMS, AND METHODS OF PATHOLOGIC RESEARCH

BY

W. M. LATE COPLIN, M. D.

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THIRD EDITION, REVISED AND ENLARGED

With Three Hundred and Thirty Illustrations and Seven Colored Plates

MANY OF WHICH ARE ORIGINAL

PHILADELPHIA

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VIAVIGLI ZMA

TO

W. W. KEEN, M.D.

PROFESSOR OF THE PRINCIPLES OF SURGERY AND CLINICAL SURGERY

IN THE JEFFERSON MEDICAL COLLEGE,

AS A TOKEN OF RESPECT AND GRATITUDE THIS

VOLUME IS DEDICATED

BY

THE AUTHOR.

PREFACE TO THIRD EDITION.

In presenting to the profession and students of medicine the third edition of this work the author wishes gratefully to acknowledge the cordial reception that was accorded the last edition. Although over twice the size of the first edition, the second was exhausted in nearly the same length of time; it appeared late in the autumn of 1897 and was exhausted in the following year.

The pressure of other duties rendered it impossible for the author to give the work the revision that seemed necessary, and therefore it has been out of print for nearly two years. During that time the author has occupied his spare moments in revising, rewriting, and rearranging the subject-matter. A number of the old illustrations have been replaced by new, and many original drawings have been added.

The author's conviction that properly prepared figures are of the utmost importance in elucidating the subject under consideration remains unchanged; in accord with this view the number of illustrations has been increased from two hundred and sixty-eight to three hundred and thirty; practically all those added are original. For the first time, a few colored plates are introduced.

The chapter on postmortems has been revised, and new methods have been introduced in the chapters on technic. Bacteriologic technic has been placed in a chapter by itself, and the technic of blood examination has been transferred to the chapter on the blood, with which it properly belongs. Special technic has been added throughout the book; whenever it was necessary to adopt any special means for demonstrating a reaction or for satisfactorily staining morbid products, the method has been

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given with the consideration of the materials to be treated. New chapters have been added, including the following: The thymus body, ductless glands, muscles, bones and joints, and the nervous system. These, added to the very much lengthened chapters originally present, have increased the size of the volume by a little over one-third.

The chapter on diseases of the nervous system has been written by Dr. H. F. Harris, Associate Professor of Pathology in the Jefferson Medical College, whose experience as a clinical teacher of diseases of the nervous system and work as an investigator have fitted him for the consideration of the subject with which the chapter deals. The author has been placed under many obligations to Dr. Harris for his supervision of the additional drawings, many of which have been made under his direct superintendence.

The author is also greatly indebted to Dr. Randle C. Rosenberger for aid in the compilation of stain reactions and biologic peculiarities of the bacteria, as well as for arranging the index of parts I and II. Dr. Frederick J. Kalteyer has aided by kindly loaning specimens for illustrations. The table on the blood occupying pages 448 and 449 is largely the product of his energy. Mr. Duncan L. Despard has assisted in the preparation of the index.

The reproduction of the new illustrations, both in black and white and in colors, has been trusted entirely to the publishers, to whom the author is under many obligations for the careful execution of this most difficult task.

In conclusion the author wishes to state that the object of the book has not been changed, and that the present edition, although greatly enlarged, remains exactly what the author intended the previous edition to be: namely, "not a treatise or book of reference, but, as its title indicates, a manual that the author hopes may be useful in the laboratory and postmortem room and in clinical diagnosis by the aid of the microscope."

PREFACE TO SECOND EDITION.

During the winter of 1894 and 1895, Messrs. P. Blakiston, Son & Co. published, in serial form, abstracts of the writer's lectures, entitled "Lectures on Pathology." At the close of the college session the fasciculi were bound, and the resulting volume placed on the market. Very much to the surprise of the publishers, as well as of the writer, the edition lasted less than nine months. It was exhausted at a time when the teaching of the college year precluded the revision which the matter so much needed. During the past six months the entire book has been revised, the larger part having been entirely rewritten. The first edition contained 250 pages and 51 illustrations; the present volume, in the face of every effort to condense without sacrificing accuracy, has reached 638 pages and contains 268 illustrations. The most difficult problem has been to keep the volume from assuming undesired dimensions, and, now that the work is completed, the writer wishes to say, parenthetically, that a volume of twice the size could have been produced with probably less labor. Being practically a new book, there are, no doubt, typographic and grammatic errors. The writer acknowledges in advance his appreciation of any communication calling his attention to such lapses.

In the publication of the original fasciculi the writer was favored by the aid of Professor Kyle and Dr. Bevan. Professor Kyle wrote the fasciculus on "Tumors," and Dr. Bevan the article on "Bacteriology." In the revision of the work both articles have been somewhat enlarged, but the thoroughness of the original has not demanded any extensive revision. There have been made some additions and a rearrangement of subjects, in order to secure greater conformity with the remainder of the

book. In the original, acknowledgment of the assistance was given with the fasciculi ; it is now incorporated here.

Practically, all the added illustrations appear for the first time in a work on pathology in the English language. The source is credited with each cut. Of the original illustrations it is not the author's province to speak. They have been prepared in the writer's laboratory from specimens and slides of which the clinical and pathologic histology were fully known. In this connection the writer wishes to acknowledge the invaluable assistance of Professor H. F. Harris, who personally superintended the execution of most of the original drawings. Miss E. G. Harding, artist, has, with great patience, made the original drawings, often redrawing an illustration a number of times before submitting it for approval.

To Drs. R. C. Rosenberger and W. P. Read the author wishes to acknowledge valuable aid in proof-reading and other detail work in the completion of the volume.

Instead of the usual method of inserting a table of illustrations, arranging the figures in the same order as they appear in the pages, an alphabetic list, by subjects, is inserted, for the arrangement of which I am indebted to Mr. L. H. Prince.

In conclusion, the writer wishes to submit the volume, not as a treatise or book of reference, but, as its title indicates, as a manual that he hopes may be useful in the laboratory, post-mortem room, and in clinical diagnosis by the aid of the microscope. To attain as fully as possible the last-named aim, the chapters on the microscopic examination of tissues, blood, and urine have been most fully illustrated.

Thanking the profession for its kindly reception of the previous edition, this volume is respectfully submitted for consideration.

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INTRODUCTION.

Pathology bears the same relation to a proper study of disease that physiology does to a knowledge of those complicated phenomena the sum total of which is called life. Physiology deals with the normal processes,—the functions of organs and tissues in health,—while pathology is a study of the causes and manifestations accompanying disease. Physiology is the science of normal life; pathology is the science of abnormal life—disease. It has been said, and quite truly, that pathology is morbid physiology—the physiology of disease. The two subjects demand associated study, as from a knowledge of one is acquired more or less information bearing either directly or indirectly upon the other. A detailed study of the intricate problems of morbid processes, and of the relations of tissue change to alteration of function, and a thorough acquaintance with the normal, render at once apparent the intimate association of pathology and physiology.

Throughout the study of pathology it is to be remembered that the changes contemplated are but perversions of the normal. Disease, with its alterations in structure and function, is not an entity from without, not an importation whose existence within the body is passive, but all morbid processes, while they may arise from causes acting from without,—causes having an existence as a part of the outside world properly so called,—are themselves essentially but perversions of normal vital activity. The same cells, or their progenitors, active in a morbid process, were the essential elements in the normal life of some tissue of the body. As the result of altered conditions the cellular activity has been perverted, and the new line of cell life is but a change in the manifestations of cellular activity—not a new, nor foreign, nor extraneous life carried on within the affected tissues. The apparent exception to this, in the growth of animal and vegetable parasites within the tissues, is not really an exception; so long as the life of the normal cells is not in any way disturbed, disease does not result; as soon, however, as the foreign elements interfere with the usual course of events, those cells performing cer-

tain functions in a manner recognized as normal for the species under observation assume a new rôle, and manifest their activity along a line foreign to their usual course. It therefore becomes evident that the diseased tissue is the result of changes in the normal, and that the cellular elements present are but modified forms of normal cells. In order properly to appreciate the significance of tissue alterations a careful investigation into the causes of disease becomes an absolute necessity; with advance in the study of **etiology** it has become possible to comprehend many diseases and fully to understand phenomena previously inexplicable.

The study of the active process associated with disease and its results implies the investigation of gross alterations,—the **morbid anatomy**; and, what is truly included as a part of the anatomy, the changes in the finer structure of the tissues—the **morbid histology.** That the study of these two divisions of the subject may have important bearing on practical medicine it is necessary to observe the relation maintained between both gross and microscopic lesions and the function of the diseased organ; this constitutes a study of **morbid physiology,** the perversion of the normal, due to, or associated with, the lesions, either gross or microscopic, themselves the active phenomena of disease; and, lastly, the pathologist must be familiar with the results following the subsidence of morbid processes.

The methods of study must of necessity vary with the morbid process under consideration. When any of the lower animals are susceptible to the disease under investigation, for evident reasons the experimental method offers many advantages. Being able to vary the conditions under which disease is induced in an animal, to kill the animal at any period in the development of the morbid process, and more fully to control external conditions, make this method in many instances of the greatest value.

Like all methods for studying disease, experimentation is open to certain objections; it is not possible in all cases fully to interpret the results, or they may not be applicable, on the whole, to man. While such important objections to the method often hold true, the author does not recall a single instance in which, after prolonged effort, it has not been possible to learn something, and in a number of diseases the method under consideration has afforded full and entirely satisfactory explanation of phenomena previously obscure or absolutely unappreciated. In many diseases all that is known has been tediously worked out by this form of research. Again, many diseases to which man is liable can not be induced in animals, and in such cases

the method fails. It has been urged that the end attained does not justify the suffering induced in the animal experimented upon. Such an objection need not be answered here, since those who hold it can not know of the advances made by the experimental methods of study, or are not in that condition of mental receptivity necessary to appreciate scientific truths. The results attained by the investigation of disease in lower animals have probably done more to alleviate suffering in them than in man.

Comparative pathology—the study and comparison of morbid processes in the lower animals and in man—also affords ample opportunity to obtain information as to the causes of, and alterations in, disease.

In all pathologic study, to attain the best results the statistical method must be used to a certain extent. The collection of a large number of cases, with a careful analysis of recorded data, can but yield valuable conclusions. The constancy of associated lesions—as, for example, the association of certain nervous and nutritive phenomena with removal or disease of the thyroid gland—often indicates a path for investigation that may terminate in a happy solution of some obscure problem.

The study of diseased organs or tissues postmortem or after removal from the body need hardly be mentioned as a most fruitful source of knowledge concerning morbid processes.

In addition to the above methods, it can not be an error thoroughly to study morbid processes during life. Therein lies the strength of the science. The symptoms of a disease are but expressions of the lesions—the morbid physiology induced by chemic, mechanical, or structural alterations. From symptoms it is possible in many cases to infer the character of the tissue changes, or, by studying the alterations in the normal chemistry and structure, the symptoms may be explained. He is far at sea who believes that the study of pathology begins and ends with the postmortem.

PART I.

TECHNIC.

PART I.—TECHNIC.

CHAPTER I.

POSTMORTEM EXAMINATIONS.

I. INSTRUMENTS NEEDED.

A postmortem may be made with a very few instruments; those supplied in an ordinary dissecting case may suffice for the examination unless the central nervous system is to be removed, in which case a saw will be found necessary. Scarcity of instruments is rarely a justifiable excuse for failure to avail one's self of an opportunity to hold a postmortem. A most thorough examination may be made with a knife such as is ordinarily used by butchers, a saw, and a carpenter's hammer and chisel.

The following list of instruments and appliances may be procured by those contemplating the making of postmortems, the extent of their purchase being largely a matter of taste and money available. The instruments marked by an asterisk are considered indispensable, the others being conveniences to facilitate or lessen the work of making postmortems:

* One Virchow postmortem knife.

* Two strong scalpels.

* Two small scalpels; one probe-pointed.

One costotome, or, when this can not be obtained, a cartilage knife or a saw may be substituted.

* At least two dissecting forceps: one with corrugated blades and one with rat-toothed blades. A number of such instruments will be found useful.

* One pair of scissors: one blade sharp and one probe-pointed.

One enterotome, or, when this is not available, a small cork or piece of wood may be pushed over the tip of the sharper pointed blade of the ordinary scissors.

Two long probes: one should have an eye and one should be quite slender; the latter is convenient for tracing ducts. An instrument to be commended is a combined grooved director and

probe. For the examination of sinuses and whenever it can be employed, there is no instrument that can be used to better advantage than the trained finger.

* One saw with a well-bellied cutting-edge.
* One grooved director.
* Two large postmortem needles.
* Two spools of flaxed thread: one white, one black.
* One mallet; the rawhide mallet has the advantage of making but little noise when used on the chisel. The steel hammer ordinarily supplied with postmortem cases has a blunt hook on the handle, which is useful for removing the calvaria, and occasionally for other purposes. The objectionable noise made by pounding on a metallic chisel may be overcome, at least partly, by covering the chisel with a folded towel.

FIG. 1. - COMPLETE POSTMORTEM CASE.
It is convenient to have a leather covering for the case.

One chisel. Of the various forms of chisels recommended, the lower one in figure 19 will be found most useful. Some of the forms of hatchet-chisel, however, will be occasionally used.

A brass or German-silver ruler, graduated in inches and in centimeters, will be found useful. Such a ruler should be at least twenty centimeters in length, and the graduation throughout should be in tenths; a finer graduation on instruments of this kind can rarely be read at the postmortem table. As a result of attempts to reduce the number of instruments contained in the postmortem case, the writer has had the long, thin-bladed brain knife, shown in figure 11, graduated along its back. As the instrument is useful for incising organs, it makes the graduation convenient and always at hand.

A double rachiotome is a very useful instrument, but is not, however, convenient for carrying around to private postmortems.

A strong bone forceps will occasionally be needed.

Measures of Capacity.—Small graduates measuring from 0.1 c.c. to 50 c.c. will be found useful. Larger measures should be at hand. Any agateware or tin vessel (the former is preferable) may be standardized by a smaller graduate, and being very much less fragile and less expensive, is therefore to be preferred.

A syringe for sucking up fluid from the bottom of cavities not easily accessible is a convenience.

In well-appointed hospitals, morgues, etc., a room is usually set apart for postmortems. This room should be well lighted and capable of thorough ventilation. The floor should be of impermeable concrete, the walls tiled or built of enameled brick, or, in the absence of these, covered by lusterless white enamel paint. A capacious postmortem table should be so placed in the room as to be well lighted and accessible on all sides. The size of the table is often a matter of individual preference. The table preferred by the writer is three feet wide, six feet long, substantially constructed, zinc or slate covered, the covering slightly raised at the edges of the table, and the top gently sloping toward a large grate-covered drain in the center. This drain, thoroughly trapped, may be directly connected with the sewage system, and may be so attached to the ventilation system as to secure a strong downward draft, thus drawing downward all odors which would otherwise rise and permeate the room. For convenience in measurements a centimeter and inch scale may be ruled upon the edge of the table.

Although never to be used when it can be avoided, an abundance of artificial light should be at command. The best artificial light for the postmortem room is afforded by Welsbach burners with porcelain reflector and shade; thirty-two candle-power incandescent lamps with thoroughly frosted globes are the next best substitute for natural light. All forms of artificial light so modify the color of organs as often to afford misleading pictures to the uninitiated.

Water-supply.—Suspended just above the autopsy table and coming down to within an inch or so of the table should be a rubber hose connected with proper metallic fixtures, so arranged as to afford a mixing device, by means of which hot and cold water can be mixed and delivered through the rubber tube at any temperature that may be desired. By permitting the rubber tube to project practically to the table the end can be kept in a pan, thus affording a small reservoir of constantly clean water. The

flexible rubber hose affords facilities for washing the table and keeping the instruments and appliances in use clean.

A capacious sink in some part of the room is desirable; into this should drain a slate dripping-slab sixty centimeters wide and two meters long.

Two scales should be at command—one for weighing from a fraction of a gram to ten or twenty grams, the other for heavier masses. Although rarely at hand, a scale for weighing bodies is desirable. Scales for weighing organs and tissues should have large brass pans that can be readily cleaned.

A head block twelve inches long and six inches square, with a notched depression near the center for receiving the neck, will be found useful in supporting the head, and similar blocks may be used for arching the body during the examination of the spine and the removal of the cord.

Heavy boards, fifty by sixty centimeters, will be found serviceable for the support of organs during section.

A vise will be occasionally needed.

Of the various forms of head holders in the market, the writer has never felt that any was better than the hand.

Every well-equipped postmortem room has a book for recording the data obtained at postmortems. This book is usually made up of printed sheets, having a heading arranged according to some definite form which has been adopted by the pathologist. Such headings are useful in making it reasonably certain that no matter who makes the postmortem, the customary routine will be followed. The volume should not contain a very large number of pages, certainly not over four or five hundred, as a large number would make it too bulky for convenient handling; nor should the sheets be too large. The book to which the writer is accustomed has a page forty centimeters long by twenty-eight centimeters wide, and has printed on each alternate page the form given in the foot-note on page 21. At the time the book is printed it is well to have two or three hundred sheets left unbound, so that at postmortems made outside the institution it will not be necessary to carry the book.

II. PRELIMINARY DATA.

Before beginning the postmortem it is desirable to know and record the name; age; residence, or, in hospital cases, the ward and bed; sex; color; date and hour of death; date and hour of postmortem; methods of preservation if any have been used; the clinic diagnosis; the name and residence of the physician, if

any, who last attended the case, and, if possible, his presence should be had at the postmortem.

In medicolegal cases the body should be identified. If the time at which death took place is not known, it may be approximated by the postmortem evidences.

III. THE POSTMORTEM.

In order that the record of a postmortem may be perfect, it is absolutely necessary to follow a definite method in each case. If circumstances demand a variation from this routine method, the *reason for varying should constitute a part of the record.* The following presents nothing original, and is the method adopted by the writer:

(A) The Date and Hour of the Postmortem.

(B) External Examination of the Body.

(*a*) *Is the body dead?* The following observations should be made and recorded as a part of the postmortem notes, as they

---

FORM OF APPROVED POSTMORTEM BLANK.

[NAME OF INSTITUTION.]

POSTMORTEM.

Ward..... Register No.....

Name, Age, and Sex of Patient..... Color.....

Physician or Surgeon..... | Residence .....

Resident Physician..... | Birthplace .....

Date and Hour of Death..... | Date and Hour of Postmortem.....

Clinical Diagnosis { ....

Pathologic Diagnosis. { ....

When possible, it is desirable that the following order of examination and recording the postmortem shall be followed:

I. External examination:
Evidence of injury. General nutrition. Ante- or postmortem marks, etc.

II. Internal examination.

1. Abdominal Wall.
2. Peritoneum.
3. Pleuræ.
4. Pericardium.
5. Heart.
6. Lungs.
7. Larynx; Trachea; Bronchi.
8. Thymus; Thyroid.
9. Spleen.
10. Adrenals and Kidneys.
11. Bladder and Internal and External Genitals.
12. Stomach and Duodenum.
13. Liver.
14. Pancreas.
15. Intestines.
16. Esophagus.
17. Vena Cava and Aorta.
18. Head.
19. Spinal Cord.
20. Miscellaneous.

cover not only the signs of death, but constitute a part of the evidence of diseased conditions: (1) Examine for evidence of respiration and circulation. (2) Look for opacity of the cornea, loss of sensibility in the conjunctiva, pupillary reaction, which may, in doubtful cases, be tested by atropin or eserin; if the eyes are sunken, with wrinkled tunics, the evidence is clear. (3) Pallor of the body may or may not be present, and while valuable as a sign of death, it may be found in the living during swooning, the algid state of ague, collapse, etc. (4) Cooling of the body to the temperature of the surrounding medium (*algor mortis*) occurs in from fifteen to twenty-four hours. The bodies of children and old and lean bodies cool quite rapidly, while bodies of fat, young, and middle-aged individuals retain the heat much longer. The bodies of persons dying from suffocation, electricity, tetanus, and yellow fever very slowly yield their heat. (5) *Cadaveric rigidity*, or *rigor mortis*, occurs at a varying interval after death. It may become manifest but a few minutes after death, or it may be delayed eighteen or twenty hours; usually, it develops simultaneously with the loss of body heat. The duration of rigor mortis is extremely variable, lasting in some instances but a few moments; in other cases, hours, days, or even weeks. (6) *Cadaveric lividity* (the cadaveric blotches called *livores mortis*) and *suggillation* are terms applied to the livid or violet-colored discoloration which is seen usually several hours after death. It becomes apparent in the most dependent portion of the body, and is the result of blood gravitating into the capillaries. (7) *Putrefaction* is an indubitable sign of death. The time at which it becomes manifest varies greatly, and is dependent upon the condition of the body, the surrounding media, and the cause of death. (8) Experimentally, we may infer that the body before us is dead by injecting ammonia water under the skin; in death such a procedure leaves no mark, but in simulated death it occasions a dark spot. A dead body can not be blistered.

(*b*) *General Considerations.*—The amount of adipose tissue, the muscular development, and the nutrition of the body should be carefully noted, and the record completed or verified as the internal examination proceeds. In case the body has not been identified an elaborate description should be made for the purpose of further identification: the height, weight, measurement of chest, limbs, hands, and feet, color of eyes and hair, and of the latter some should be preserved. A careful survey of the mouth as to dental peculiarities, absence of teeth, filled or irregular teeth, or, better, a dental impression taken in wax or plaster. If false teeth are present, they should be removed as

possible aids to future identification. Abnormalities, malformations, marks of any kind, should be noted, and, when possible, a photograph should be obtained. Such data may, with perfect propriety, constitute a part of any postmortem record; indeed, they are desirable although rarely incorporated in the protocol. Except in the cases mentioned they might have little value in any given postmortem, but in the compilation of important data based of necessity on a large number of cases—*e. g.*, the size and weight or organs as compared with the height and weight of the individual—such records would become invaluable.

(*c*) *Evidence of Violence or Disease.—Ecchymoses* should be carefully described as to size, shape, and position. This form of discoloration may be distinguished from *suggillation* in that it does not disappear on pressure, and if an incision be made into it, bloody fluid will escape, or a clot may be discovered in the subcutaneous tissue. All abrasions, eruptions, bed-sores, ulcers, cicatrices, wounds, edema, pigmentations in the skin and mucous membranes must be accurately described, and their positions carefully recorded. Fractures and dislocations must be closely observed, and their character and the parts involved noted. The external orifices of the body should be examined, and their condition and contents noted—*e. g.*, mouth and nose for foreign bodies, evidences of corrosive poisoning, etc.; in the female, the breasts, abdomen, and external genitals should be examined for evidences of disease, violence, or physiologic processes, such as menstruation, recent delivery, or evidences of past gestation, as shown by the mammæ, abdomen (linea alba), or external genitals; in the male look for evidence of malformation of the sexual organs or venereal disease, also seminal stains. Examine the anus for fissures, inflammation, fistulæ, morbid growths, cicatrices, etc. Examine the hernial outlets for evidences of rupture. If the body is that of an infant, examine the fontanels and sutures, and note the various diameters of the skull. Measure the body and examine the umbilical cord. In the male the scrotum should be examined to determine if the testicles have descended; note, also, the presence or absence of vernix caseosa. Carefully examine the epiphyses, and especially that of the lower extremity of the femur.

(C) Internal Examination of the Body.

The large Virchow knife is used for most of the incisions; it is grasped firmly in the hand by the thumb, middle, ring-, and little fingers, while the index-finger rests upon, or at the side of, the blade. Cuts are made with a drawing movement, the shoulder- and elbow-joints acting as centers, the wrist and

fingers rigid. Pushing the knife through a tissue or organ, as one would a chisel, is to be avoided, and equally objectionable are sawing and hacking. In ordinary dissection a scalpel is held like a pen, motion being at the joints of the fingers and wrist—a process entirely too tiresome and slow for postmortem work except when very delicate dissections are to be made.

The body rests firmly upon the back, and the operator, if right-handed, stands upon the right of the cadaver. To expose the abdominal and thoracic cavities, an incision should be carried from the lower border of the thyroid cartilage, or from the interclavicular notch, to the symphysis pubis, making a sharp semicircular turn to the left at the umbilicus in order to avoid injury to the remains of fetal organs at that point. The point in the neck at which to begin the incision will be determined by circumstances over which the operator quite frequently has no control. If he can select the starting-point of his incision, he will ordinarily begin just under the chin, or may even make a Y-shaped

FIG. 2.—MODIFIED VIRCHOW POSTMORTEM KNIFE.
Twenty-four centimeters long, of which 9.5 cm. is cutting-edge.

cut extending to the angle of the jaw on either side; this permits a most careful examination of the floor of the mouth, pharynx, larynx, and adjacent structures. So extensive a mutilation is rarely demanded; in most instances the loosened skin can be retracted upward in such a manner as to permit the removal of the tongue when the vertical incision does not rise above the level of the thyroid cartilage. Still, as before stated, circumstances will more commonly settle this point than any arbitrary rule.

Over the abdomen, the first incision should pass through the skin and subcutaneous tissue; then carefully cut through the abdominal wall immediately below the ensiform cartilage; insert two fingers of the left hand, drawing the abdominal wall upward; continue the incision, the fingers being used as a guide to the knife. A most excellent rule, never to be forgotten by the beginner, is to always keep the point of the knife in view, or, if this is not possible, it should be guarded. If the novice makes it a rule never to cut anything until he has determined what it is and what are its relations, using touch possibly more than sight

to determine these facts, he will often be astonished at the dexterity which he quickly acquires and the rapidity with which his senses become trained to recognize the tissues before him. Note

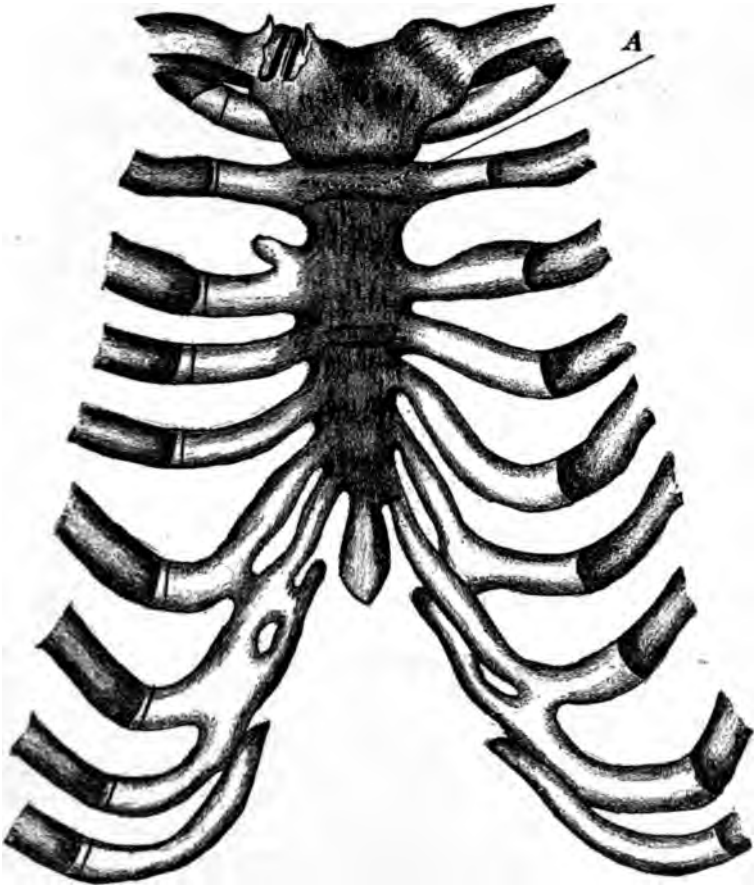

FIG. 3.—THE STERNUM, COSTAL CARTILAGES, AND ARTICULATION OF THE CLAVICLE, AS EXPOSED AFTER TURNING BACK THE SOFT PARTS.—(*Modified from Virchow.*)

On the left is shown the line of incisions made through the cartilages from below upward, if a costotome is used; from above downward, if a knife or saw is employed; and also the incision necessary for disarticulating the clavicle. When it is not desirable to disarticulate the clavicle, the manubrium is separated from the gladiolus at point *A*, the incision being made from behind.

the amount and color of the subcutaneous fat in the abdominal wall, its consistency, and the presence or absence of edema. Examine the muscles for pallor, hyaline spots, degenerative

changes (such as occur in typhoid fever), and small white ovoid bodies, encysted trichinæ. Dissect the tissue from the chest-walls as far back as the junction of the costal cartilages with the ribs; then make strong traction on the abdominal walls to break up the rigor mortis. After breaking up the rigor mortis the muscles can be further incised, and examined for evidences of bruises, inflammation, and suppuration, and suspicious portions removed for microscopic study.

Abdominal Cavity.—First note the relative position and color of the liver, stomach, and intestines; and also the relations of the viscera to the costal and ensiform cartilages. The examination of the cavity is not of the organs individually, but of their relation to one another and to the walls; also examine the serous membrane—the peritoneum. A careful search should be made for adhesions and other evidences of inflammation, recent or old,

Fig. 4.—Costotome.

and for thickening and opacity of the serous membrane. The amount and character of any fluid in the cavity must be noted, and, if in excess or abnormal in character, the source or cause of the morbid condition must be sought. The color of the liver should be observed before those changes incident to the oxidation of the blood occur. Search carefully for perforations of the bowel, stomach, bladder, or gall-bladder, whenever the fluid in the cavity is abnormal. Note accurately the position of the diaphragm: ordinarily, on the right side it ascends as high as the fourth rib or interspace; and on the left, to the fifth rib. Remove any fluid present in the cavity before going to the thorax, as fluids in the abdominal cavity would flow into the thoracic cavity and thereby complicate the examination.

Thoracic Cavity.—With a heavy knife, or costotome (or, in the absence of the latter, when the cartilages are calcareous, a

saw may be used), sever the costal cartilages close to the ribs, care being exercised not to injure the tissues beneath. If the costotome is used, the blade inserted beneath the cartilage should be made to hug that structure closely; if a knife or saw takes the place of the costotome, the incision through the cartilages should begin above and before one cartilage is completely severed, the blade or shank of the instrument should be made to rest on the next cartilage, thus preventing sudden thrusts which may wound underlying structures. When the last cartilage is reached, it should be gently raised by the unoccupied hand, at the same time depressing the underlying structure, thereby avoiding the danger of wounding the latter.

Divide the attachment of the diaphragm, raise the sternum, and dissect off the attached tissue, taking care to direct the edge of the knife toward the bone in order to avoid injury to the pericardium or other intrathoracic tissues. Cut the ligaments which bind the clavicle to the sternum, divide the sternal attachment

FIG. 5.—Saw.
A large firm handle is wanted, with good pistol grip.

of the sternocleidomastoid muscle, and pull the breastplate to one side. In a cadaver in which the section of the thorax has been made as just directed, the shoulders, having lost the support of the clavicle through their sternal attachment, collapse together, making the chest appear very much distorted. To avoid this, in cases where the body is to be viewed, it is suggested that the manubrium and gladiolus be disjointed, which may be accomplished by drawing the edge of the knife across the under surface of the articulation of the manubrium and gladiolus (see Fig. 3, p. 25) and raising the lower segment of the sternum.

Examine the pleuræ for evidences of inflammation, either remote or recent; note presence or absence of fluid, also its quantity and character, as in the peritoneum. Fluid in each pleura should be removed, so as to prevent its flowing into the pericardium; or, in case the pericardium contains much fluid and any escape into the pleura, its quantity may be accurately estimated. The fluid in each cavity should be measured, and the

quantity made a part of the record. Adhesions should be looked for and described. The pericardium should now be opened by an incision extending from base to apex in a line parallel to the long axis of the heart. In opening the pericardium the writer has seen the heart injured so often that he desires to insert a

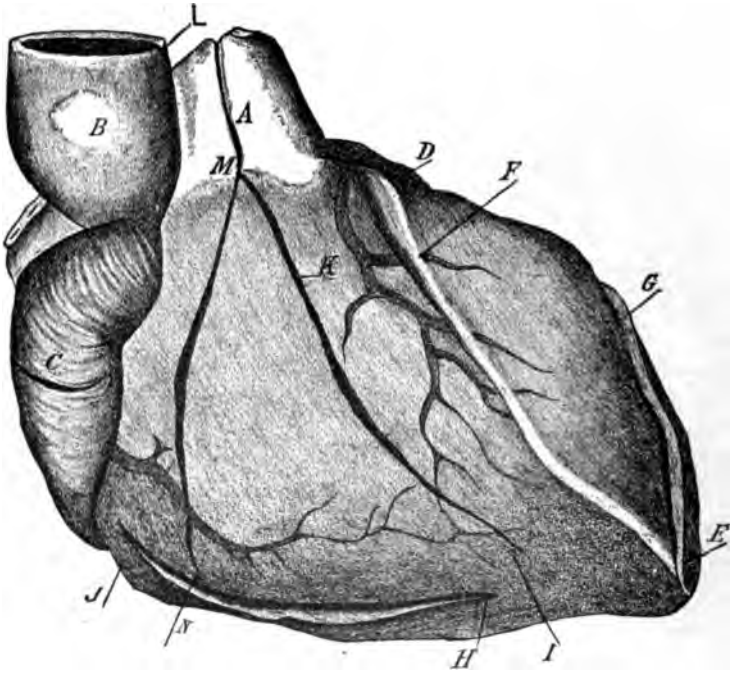

FIG. 6.—HEART SHOWING THE LINES FOR INCISIONS IN THE PRELIMINARY EXAMINATION AND FINAL SECTION, FULLY EXPOSING THE VALVES.—(*After Virchow.*)

A, Pulmonary artery. *B*, Aorta. *C*, Right auricle. The incision *M* to *N* is that advised by Virchow. The one preferred by the writer is from *K* to *I*, for the preliminary opening of the right ventricle. The preliminary opening of the right auricle is made at *C*. The preliminary opening of the left auricle is made at *D*. The preliminary opening of the left ventricle is made at *F* to *E*. After the heart is removed, the incision made at *C* is carried out through the vena cava; the incision from *K* to *I* is carried through the pulmonary artery between the letters *M* and *A*, and below is carried around by *H* to *J*. The incision *M* to *N* is not made. The incision *F* to *E*, in the left ventricle, is carried around behind the pulmonary artery, *A*, and comes out in the aorta at *L*. From the lower portion, at *E*, the incision is carried upward to about where the letter *G* is shown; this permits the flap to be turned back so that the mitral valve may be examined; the incision made may then be carried through the mitral orifice.

word of caution and give a little more detailed method for preventing this accident. The pericardium is picked up in a fold either by the index- and fore-finger of the left hand or by the use of "rat-toothed" forceps; by gentle traction this fold of the pericardium can be raised to a distance of 2.5 cm. The back

of the knife is now placed against the heart and the fold, made as previously directed, is transfixed and the opening completed by cutting from within outward. A similar incision has been long recommended by surgeons while operating upon hernia when wounding of underlying tissue may be attended by calamitous consequences, and if applied to the pericardium with but slight precaution, wounding of the heart may be entirely avoided. From this incision, which is two or three centimeters in length, the

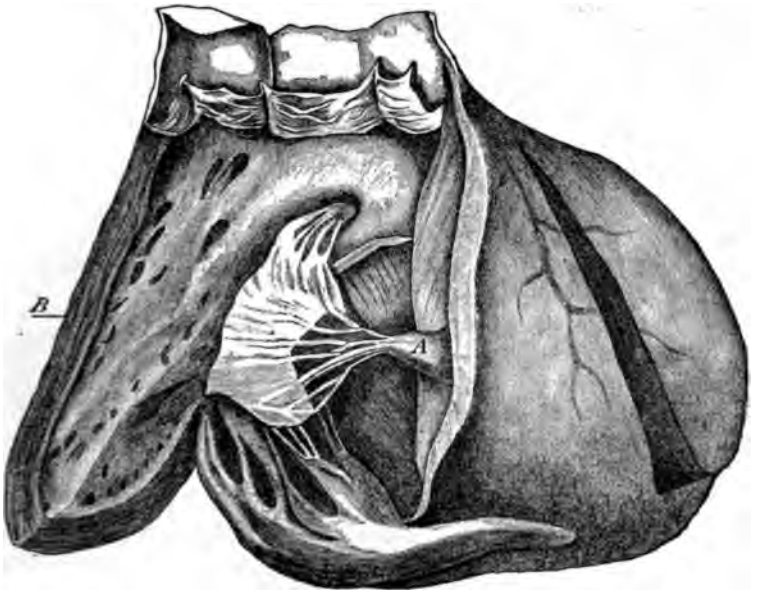

FIG. 7.—HEART SHOWING THE INTERIOR OF THE RIGHT VENTRICLE AND PULMONARY ARTERY.—(*After Virchow.*)

If the incision *M* to *I*, figure 6, be made as advised by the writer, the papillary muscle (*A*) will be carried over with the ventricular wall (*B*), thereby better exposing the auriculo-ventricular orifice.

incision in the long axis of the heart, as previously directed, may be readily made. Incisions at right angles to the long incision are rarely, if ever, demanded; the writer does not recall an instance in which he has needed a larger incision than that afforded by the opening extending from the apex to the great vessels. Examine the layers of the pericardium for evidences of inflammation, and look carefully for adhesions, particularly about the great blood-vessels. Measure the pericardial fluid and note its character. The heart should now be examined. Note the con-

dition of contraction or relaxation of the heart's wall; open the heart *in situ;* raise the organ by its apex, pass the fingers of the left hand under the organ, and so grasp it that the thumb and first finger will close the auriculoventricular orifice of the right side, and then make an incision into the auricle between the venæ cavæ. Examine and note character of contents; without relaxing the grasp on the auriculoventricular orifice,

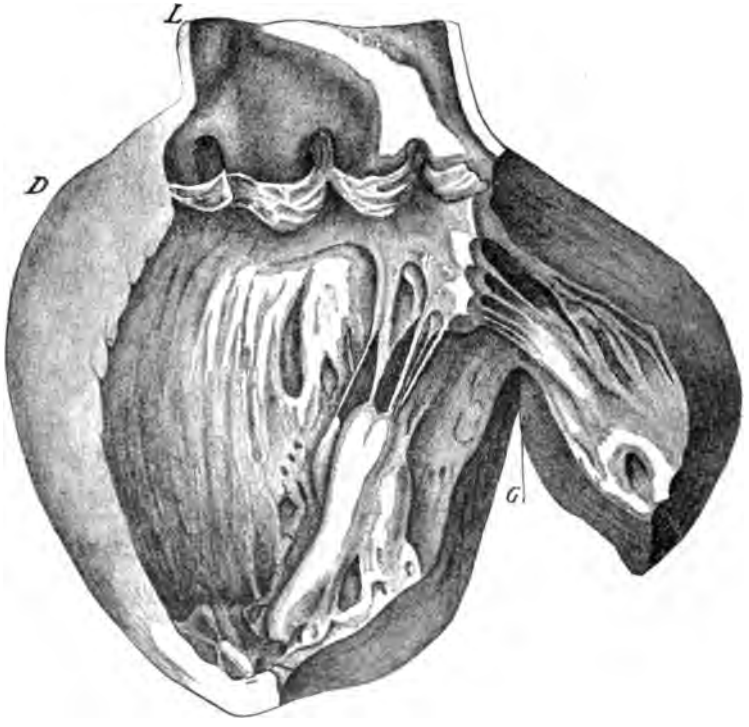

FIG. 8.—HEART WITH THE LEFT VENTRICLE LAID OPEN, SHOWING THE AORTIC CUSPS AND THE VENTRICULAR ASPECT OF THE MITRAL VALVE.—(*After Virchow.*)
The letters have the same significance as in figure 6.

open the right ventricle by an incision in line with the pulmonary artery and close to the ventricular septum; insert the index-finger of the right hand and examine the contents. The left heart is opened by grasping it as in opening the right. The auricle is incised near the appendix and immediately above the auriculoventricular septum, and its contents are noted. The left ventricle is opened by an incision almost parallel to the opening

made in the right ventricle, but on the opposite side of the septum, and the incision is directed toward the aorta. The presence or absence of blood or clots in the left ventricle must be carefully noted. Examine the great vessels as to abnormality, aneurysm, or other disease discernible externally. In the newborn it may be advisable at this time to trace the pulmonary artery and aorta, demonstrating the relation of one to the other, and the condition of the ductus arteriosus. Remove the heart, dividing the great vessels from below upward, severing the aorta last. Test the valves as to competency, being sure to wash out all clots before making the test. Measure the valvular orifices. Enlarge the incisions already made so as to be able to examine

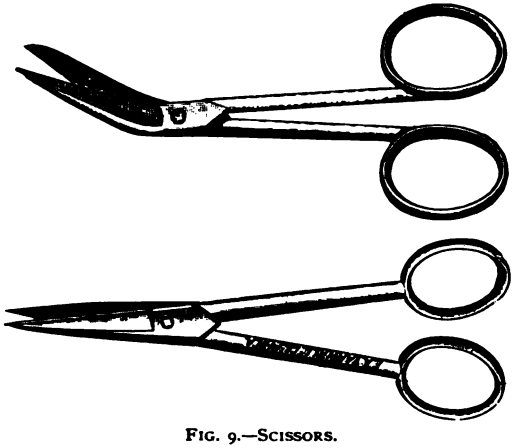

FIG. 9.—SCISSORS.
Those shown in the upper cut will be most useful, particularly if the blade shown in the cut as having the sharper point be slightly probe-pointed.

the endocardium in detail. Carry the incision in the right auricle out through the two cavæ; prolong the incision in the right ventricle through the pulmonary artery and the incision in the left ventricle through the aorta. The left auricle is opened by continuing the incision already made into the pulmonary vein. Note any vegetations on the valves, thickenings or opacity of the endocardium; examine closely the condition of the foramen ovale. State the general appearance of the cardiac muscle.

Examine coronary arteries by passing a director into each in turn, and, with knife or scissors, opening the artery as far as possible. Probe-pointed scissors may be used to advantage, and if the probe-pointed blade is small, the arteries may be opened even to their smaller branches. Weigh the heart.

Both lungs may be removed at once. Adhesions must be carefully broken up; this can usually be accomplished by the fingers alone; occasionally, however, the knife or scissors (preferably the latter) will be necessary. If the organs are adherent to the diaphragm, it is best to detach the latter from the ribs and remove it with the lung; often only a patch will require removal, at other times the entire diaphragmatic pleura may be adherent. Incise the great vessels as they pass out of the thorax; cut through the trachea, being careful not to injure the esophagus. Gentle protracted traction will strip the organs from the tissue behind, bringing forward with the pericardium the aorta, which must be severed at the diaphragm. If it is desired to leave the aorta, this can easily be done by separating it from the pericardial attachments before delivering the lungs. When removed singly, the left lung is removed first. Note the general appearance, color, and condition of the lung. The incisions made in the lung should be conspicuous by reason of their length, and the longer, other things being equal, the better. To

FIG. 10.—GROOVED DIRECTOR.
Useful for opening arteries, tracing sinuses, ducts, etc.

accomplish this, it is best to use a long section knife, which should be exceptionally sharp, making an incision from apex to base, extending through all the lobes in a line corresponding, as nearly as possible, to the axillary aspect of the organ. Lay open and dissect down the bronchi, and carefully examine their condition, a sharp lookout being maintained for the presence of foreign bodies. Note the appearance of the peribronchial glands. Weigh each lung separately.

Examine larynx, trachea, bronchi, and thymus and thyroid glands. The examination of these structures is usually best accomplished after their removal *en masse*, together with the contents of the floor of the mouth and the pharyngeal wall. If the primary incision was carried to the chin, but little difficulty will attend the removal of these organs; on the other hand, if they must be removed subcutaneously, considerable difficulty will be encountered. The skin must be carefully dissected from the underlying tissues, and a long-bladed knife passed from below upward, entering the floor of the mouth as far anteriorly as possible, making an incision laterally on both sides along the

rami of the lower jaw. The mouth is then opened widely, and the incision carried backward and upward, detaching the soft palate from the hard palate, and at the same time freeing the tonsils. The removal of this mass is accomplished by pulling the esophagus and larynx downward, pushing a long-bladed knife up behind the esophagus, and severing posteriorly and laterally the pharyngeal wall as high as possible. After removal the esophagus may be dissected from the larynx, and examined later, with or after the stomach, or it may be at once severed near the diaphragmatic opening, a ligature being applied to prevent the escape of the stomach-contents. If removed with the adjacent structures, it is opened on the posterior aspect, the larynx and trachea being opened anteriorly.

The incisions should be made through the longest diameters of the thymus and thyroid glands, as most of the lesions in these structures will be more important from a histologic standpoint than from their gross anatomy.

ABDOMINAL VISCERA.—The *spleen* is now removed. This is accomplished by gently lifting the organ out of its normal bed, pulling it forward, and severing the blood-vessels close to the hilum. As a result of past peritoneal inflammation, diaphragmatic pleurisy, or inflammation of some adjacent viscus or tissue, as the colon or perirenal structures, the spleen may be anchored by firm adhesions of its capsule to adjacent structures. Under such circumstances it is best to dissect the organ out with very great care, as protracted or violent traction may cause rupture of the organ; and if it be softened as a result of infectious diseases or other cause, the entire splenic pulp may be forced through a comparatively small opening in the capsule of the organ. Its general appearance described, make one long incision through the back of the organ down to the hilum. Note color and consistency of parenchyma, prominence of the Malpighian bodies, and stroma. Weigh the organ.

The Kidneys.—Ascertain whether both are in their normal positions, if possible. The left suprarenal body and left kidney are next examined. As a rule, the adrenal and corresponding kidney may be removed together. This can readily be done simply by tearing the peritoneum along the upper and posterior border of the kidney and gently dissecting with the fingers the connective tissue which holds the adrenal in place. Raise the kidney from its normal position, note condition of blood-vessels and incise them; examine ureter and sever it. With very little effort the ureter may be traced downward to the bladder. This should be done before severing the kidney, as later it may be

quite impossible to demonstrate that the canal contained no obstruction. The perirenal fat should be carefully removed from the kidney and the surface of its capsule accurately described before incising it. Hold the kidney in the left hand, with the pelvis directed toward the palm, and with one sweep of a sharp knife incise, from the cortex to the pelvis, in the long axis of the organ. On section, note consistency, color, the relative proportion of cortex and pyramid (normal cortex equals one-half the pyramid); the condition of capsule, whether thickened, tense or flaccid, or adherent to cortex; also note appearance of stripped surface of cortex, whether smooth or rough, etc. Examine pelvis of kidney, and weigh the organ. The same process is repeated upon the opposite side.

Examine *bladder and internal genitals.* The technic of this examination depends largely upon the conditions present. When the examination of the upper urinary tract (kidney and ureter) has led to any suspicion of disease, it is best not to detach the kidney from the ureter or ureter from the bladder until the

FIG. 11.—LONG, THIN, BRAIN KNIFE, OF VALUE FOR INCISING ORGANS.
Originally designed for brain dissection, but at present used for incising kidney, liver, spleen, tumors, etc. As shown in the illustration, the instrument should not have a cutting-edge measuring less than sixteen centimeters. The graduation along the back of the knife affords a convenient measure. On the other side the graduation is in inches.

examination has been completed. The examination of the pelvic viscera can usually be best accomplished after evisceration of the pelvis. It is best, however, to open the bladder and examine its contents before eviscerating, and in the female, when there is any question of criminal abortion, a thorough examination should be made by finger and speculum, using no cutting or probe-pointed instrument of any kind until wounds have been excluded as far as it is possible to do so before the examination is completed. Evisceration of the pelvis is best accomplished by an incision anteriorly, under the pubic arch, hugging the true pelvis posteriorly, and removing the rectum with the other contents of the pelvis. The testicle may be removed without any external incision in the scrotum by simply dissecting the skin anteriorly from the pubes and pulling the testicle by the spermatic cord gently up into the wound, from which it may be removed, if necessary dissecting the cord around to the seminal vesicles. The penis may be simply retracted through the floor of the pelvis, and removed with the prostate and bladder.

The removal of these organs without the full consent of the deceased's family should never be made, as the excision of the genital organs is always looked upon as having been done merely to gratify morbid curiosity, and exactly why it is always discovered seems very hard to determine; the fact remains that the uninitiated have been severely censured for the removal of the external genital organs, even in cases where it was perfectly justified by the findings and where it was necessary to exclude other possibilities.

The rectum should be dissected from the posterior wall of the bladder in order to expose the prostate and seminal vesicles. In the female, as this is not necessary, the rectum is opened on its posterior aspect, the vagina laterally, and the urethra and bladder anteriorly, thus permitting all the parts to be restored to their normal relation with each other. The opening on the lat-

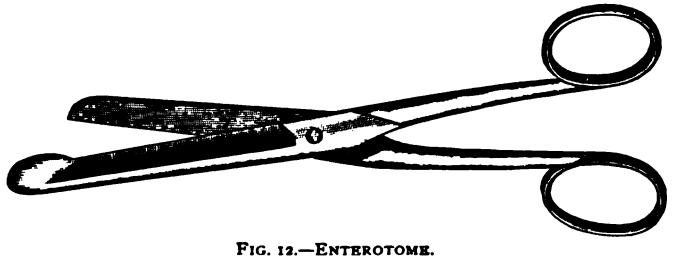

FIG. 12.—ENTEROTOME.

Useful for opening stomach, duodenum, intestines, etc. Not uncommonly the blunt-pointed lower blade is so made that it forms a tooth, like the barb on a fish-hook, and when introduced, can not be withdrawn. Never purchase such a hook-pointed enterotome.

eral aspect of the vagina is carried anteriorly at the upper end and continued through the cervix and body of the uterus in the anterior wall. If urine be present in the bladder, its character and quantity should be noted, and it should be preserved for future examination.

The left semilunar ganglion is examined, and any firmness or inflammatory signs noted. The ganglion should be preserved for microscopic examination. The corresponding organ of the right side is next in order of examination.

The Stomach and Duodenum.—In cases where poisoning is suspected, ligatures are tied at the cardiac extremity of the stomach and the upper end of the duodenum, and the organ removed; in order that the contents may be carefully examined, the stomach, without opening, should be placed in a clean jar and sent to the chemist. In case it is decided to open the duodenum and stomach *in situ*, as is best when the question of poison-

ing does not enter into the case, make an incision along the anterior surface of the duodenum and greater curvature of the stomach. Examine contents, condition, and appearance of mucous membrane. Foreign bodies are frequently met with in the stomach. Determine if the bile-duct is patulous by pressing upon the gall-bladder and watching for the escape of bile. In case this simple procedure does not reveal the presence of the ampulla and demonstrate that the cystic and common ducts are patulous they should be carefully dissected out. This can not be done after the removal of either the duodenum or liver ; as it is important in many, if not all, cases to assure one's self of the condition of the hepatic, cystic, and common ducts, and as cutting through either of them may render later demonstration unsatisfactory or even quite impossible, they should, therefore, be dissected out *in situ*. Open the ductus communis choledochus, examine mucous membrane, and continue the incision upward into the gall-bladder and hepatic duct.

The portal vein, hepatic vein, and vena cava may be opened before the removal of the liver ; or, as the first two must be severed during the removal of the liver, they may be examined at that time.

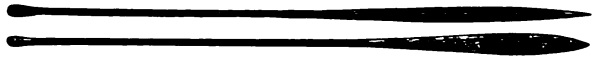

FIG. 13.—PROBES.
These should be at least fifteen or twenty centimeters long. One should be very slender.

The condition of their contents and appearances of their walls must be noted.

The *liver* may now be detached from the diaphragm, or, if it is adherent to that structure, the two may be removed together ; when the lung, liver, and diaphragm are fused by adhesions at their points of contact, and when there may be any suspicion of a suppurative lesion burrowing in either direction, it may be best to let the lung remain *in situ* until the proper time for the removal of the liver, when the three structures may be removed together ; neither the lung nor the liver should be sacrificed, but only that part of the diaphragm immediately involved need be removed with the attached viscera. The shape and color of the liver and any deformities of the lobes should be noticed, the anterior margin examined, and its condition recorded. The incision made to disclose the interior of the liver should be a long, sweeping cut, on the superior aspect of the organ, extending through the longest axis, including both right and left lobes and sufficiently deep to permit the folding of the two parts without tearing the narrow band of tissue which holds them together on the in-

ferior surface of the organ. On section, the firmness or resistance should be noted; also the color, whether uniform or mottled, and whether or not bile staining be present. Weigh the organ.

The *pancreas* may now be removed, and any peculiarity or change carefully noted.

The *esophagus* should next be examined, and the *intestines* removed. The latter should be carefully opened, and the con-

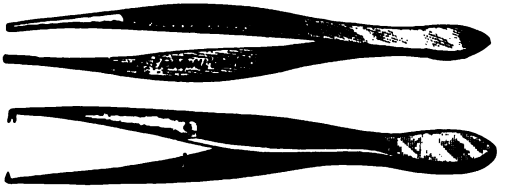

FIG. 14.—DISSECTING FORCEPS.
One of these should be toothed. These will be needed in the finer dissections, as in tracing the hepatic duct, portal vein, and receptaculum chyli.

tents examined as the incision is gradually extended. After the incision made by the enterotome has been concluded the mucous surface should be gently washed by a slowly flowing stream of water, and examined for inflammation, ulcers, cicatrices, perforations, constrictions, etc. It is probably best to open the intestines before washing them out, in order to more accurately determine their contents, examine for animal parasites, locate

FIG. 15.—MALLET OR HAMMER.

foreign bodies, etc., but cleanliness and convenience often lead to an unwise reversal of the proper order. In cases of suspected poisoning the intestines should be sent, unopened and in a clean jar, to the chemist.

The *thoracic duct* should now be traced, and the *receptaculum chyli* examined; also the *mesenteric and retroperitoneal glands.*

The *aorta* and its branches may now be examined in detail.

THE HEAD.—Insert the scalpel, with its back toward the skull, just behind one ear, and carry an incision across the vertex, cutting from within outward. If the knife is not too sharp, the hair may be parted and thrown backward and forward as the hand and knife are withdrawn. The incision should be far enough back to be invisible from the front when closed. The scalp is reflected forward and backward from this incision as low as the superciliary ridge in front and the occipital protuberance behind.

In many cases great care must be used to avoid a tear at or around the ear, as tension is produced by pulling the anterior and posterior scalp-flaps down; to avoid this unsightly tear,

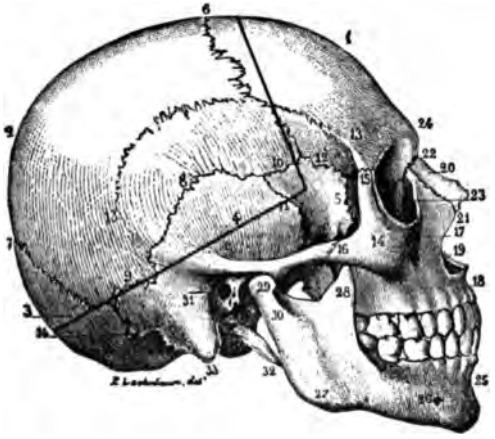

FIG. 16.—HEAVY LINE INDICATING COURSE TAKEN BY SAW-CUT IN SO-CALLED UNDERTAKER'S METHOD.

It is possible that the base line as drawn in this illustration is too low; however, this is immaterial, as the method is under all circumstances to be avoided.

which may run down in front of the ear, insert the knife under the skin, in the incision already made, just behind the ear, and dissect the skin free from the deeper structures behind and in front of the ear. The scalp-flaps, as already described, do not include the temporal fascia or muscle, which is now cut through and reflected in the line of the contemplated saw-cut. Sawing is greatly facilitated by having all soft tissue free of the line of the contemplated cut, as the soft parts clog the teeth of the saw. When the skull-cap is replaced, the fascia and the muscles may be sewed together, thereby securing the bone in place—a matter of great importance in private postmortems when the body is to be exposed at a funeral or to friends.

Inspect the skull for evidence of injury or disease. In opening the skull there are three methods of procedure—one should never be used when it can be avoided, one may be used in a few cases, and one is applicable in the vast majority of instances: (1) The "undertaker's cut" consists in sawing across the forehead just back of the hair line, from one temporal fossa to the other, and carrying a second saw-cut around the posterior base, parallel with the base line, joining the anterior cut in each temple. This method does not permit of satisfactory removal of the brain. (2) The second method should always be used in medicolegal cases, and whenever the question of fracture may arise. It does not demand the use of a chisel, and affords

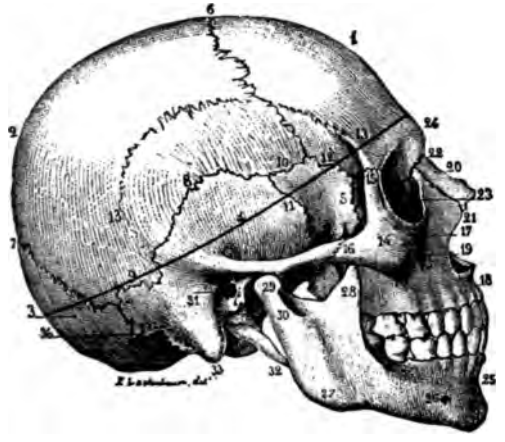

FIG. 17.—CIRCUMFERENTIAL SAW-CUT, TO BE PREFERRED IN ALL MEDICOLEGAL CASES. The exact location of the line will vary slightly, depending upon the conformation of the skull. It is usually about as indicated above.

abundant opportunity for examining the skull's interior. A circumferential line is drawn around the base of the skull, on a level with the superciliary ridge in front and the occipital protuberance posteriorly, and the skull sawed through at this line. (3) The third method, and the one most commonly employed, consists of a V-shaped incision; as viewed laterally, the anterior arm of the V is parallel with the base of the skull, on a level with the superciliary ridge, and extends backward as far as ½ of an inch behind the external auditory meatus. The other arm of the incision passes obliquely across the vertex just back of the incision already made in the scalp. It may be necessary to break out the angles of the saw-cut with a chisel; care must

be used not to mutilate the ear in making the saw-cut. The adjustment and retention of the calvaria in place may be further aided by making the posterior saw-cut also V-shaped. The angular junction of the two lines which form the V are directed upward, something like the occipitoparietal suture. To repeat: This makes two V-shaped saw-cuts as follows: Viewed laterally, the anterior arm of the first V is parallel with the base line, and extends from the superciliary ridge to just behind and above the external auditory meatus, the posterior arm of this V being subdivided into the two arms of a second V, which, as viewed from behind, is upside down. The advantage of this incision lies in

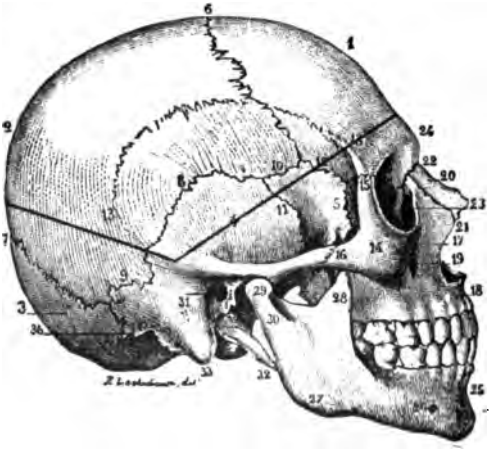

FIG. 18.—WEDGE-SHAPED CALVARIA REMOVED BY THE LINE OF SAW-CUT RECOMMENDED. (See Text)

If the posterior cut is so made, from the right and left sides, that the point just above the figure 7 will be the apex of a triangle, two sides of which are formed by posterolateral saw-cuts, there will be no difficulty in retaining the wedge-shaped calvaria in place.

the easily adjusted calvaria, the wedge-shaped cap being readily replaced and secured in position, so that no external evidence of the postmortem will be visible when the scalp is returned to place and sutured.

Inspect the interior of the calvaria for evidence of injury or disease, noting its thickness and the condition of the diploe and of the external and internal tables. The dura may be removed, or, rather, reflected back, by incising it along the lower saw-cut and detaching the falx cerebri from the crista galli. When, as in the very young, it may be necessary to remove the dura with the calvaria, it will only be necessary to incise the dura along

the line of the saw-cut, and to sever the falx anteriorly and posteriorly before making any attempt to raise the calvaria.

Inspect the surface of the brain for superficial injuries or disease, but make no incision into it. It may here be necessary to note the relation of brain landmarks to the skull, fixed points of the latter being selected for the comparison.

The brain is next to be removed, beginning in front by carefully raising it from the base, being sure to raise the olfactory bulbs with the hemispheres; still cautiously elevating the hemispheres, sever the nerves as they pass out of the skull, those in front first, and then in order as they appear. When the tentorium is reached, detach it from the temporal bone and follow the base, severing the nerves as they find exit from the posterior

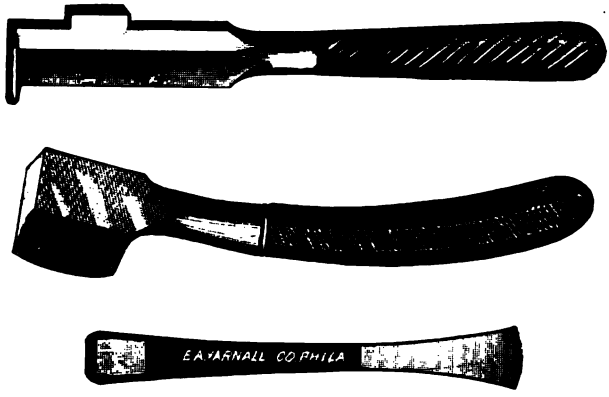

FIG. 19.—CHISELS.
If only one is to be purchased, the lowest one will be of most use.

fossa; lastly, pass a long, slender-bladed knife along the basilar process of the occipital bone, and down into the spinal canal, cutting the cord as low as possible. In order to section the cord as nearly transversely as possible and to avoid the oblique incision made in the manner just directed, some operators prefer the use of a myelotome. After section of the cord the entire brain can be easily removed. Complete the examination of the interior of the skull, noting the condition of the bone, blood-vessels, sinuses, etc., dissecting the dura from the base to facilitate the examination of the bone. Before detaching the dura the contained sinuses should be slit up and examined for evidences of thrombi, septic processes, etc. The posterior part of the orbit and the eyeball may be examined by chiseling the roof; in the

same way examine the frontal, sphenoid, mastoid, and ethmoid sinuses and the internal ear.

The *brain* should be, in most instances, hardened before dissection; if this can not be done, immediate examination may be made as follows: Make a careful examination of the meninges, and note the color, consistency, etc., of the external surfaces, including the base; the consistency is best determined by gently palpating the entire cortex. Examine the blood-vessels at the base,

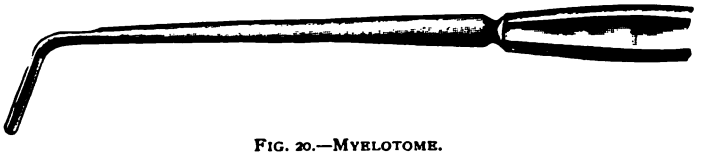

FIG. 20.—MYELOTOME.

Used for separating the brain from the spinal cord. The advantage claimed for this instrument is the facility with which the cord may be cut transversely, thereby avoiding the objectionable oblique incision which is usually secured when the ordinary knife is used for the same purpose.

tracing them into the brain-tissue. An incision is made on each side, just over the corpus callosum, into the lateral ventricles, and continued backward and forward, that they may be carefully inspected; the amount and character of the fluid present are noted. The lateral ventricles are joined by an incision through the fornix, reflecting the corpus callosum backward, exposing the tissues beneath. Search for hemorrhages, areas of softening, tumors, inflammation, abscesses, etc. Lateral

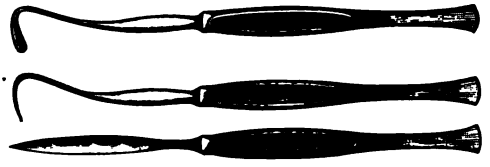

FIG. 21.—SCALPEL WITH BLADE SHAPED SOMEWHAT LIKE A BISTOURY.

Useful in removing the brain and spinal cord. The aneurysm needle and tenaculum shown are useful at times, but are not essential.

incisions are now made in the cortex from the ventricle outward, so as to note the condition of the cerebral substance; the incisions should be parallel, not over one centimeter apart, and the membranes should not be cut through, as they will retain the cut parts in position. The brain is then turned over, and the tissue of the base examined by transverse incisions through the medulla, cerebellum, etc., examining for such changes as previously noted. Weigh the brain.

While occasionally much information can be obtained by the gross examination of a freshly removed brain, improvements in histologic technic have made the microscopic examination of greater importance. In order to obtain valuable information from this method, it is necessary to secure sections which permit of the rebuilding of the organ, so that the connection between different parts may be traced. This implies the use of some serial method similar to that employed in embryologic work. The size of the human brain precludes satisfactory serial sections of the entire mass, and as the serial sections are for the purpose of demonstrating histologic lesions in paths or bundles, each case will become to a certain extent a law unto itself. For the study of the neuroglia immediate fixation in special fluids is necessary (see section on Nervous System), and for the demonstration of different lesions a different technic may be required.

The Pitres-Nothnagel Method.—The lateral ventricles are opened as described; the pons and cerebellum are severed by section of the peduncles; the cerebrum is divided by a vertical section (longitudinal) through the median line—the third ventricle; each half of the cerebrum is then incised from above downward, transversely to its long axis and as nearly as may be parallel with the fissure of Rolando: (1) Five centimeters in front of fissure of Rolando; (2) through posterior margin of the frontal convolutions; (3) through ascending frontal convolution; (4) through ascending parietal convolution; (5) three centimeters posterior to fissure of Rolando; (6) one centimeter in front of parieto-occipital sulcus.

The fixation of each of these sections completed, serial sections are made from each area. While much more tedious and requiring greater care, this method permits of reconstruction and the adaption of parts so as to follow fillets, or paths, with a precision not possible by the cruder methods.

For demonstrating the condition of the blood-vessels at the sacrifice of everything else, the brain may be gently washed away and the blood-vessels floated out in a basin of water.

THE SPINAL CORD.—The body is turned upon the abdomen, and blocks are so arranged as to arch the vertebral column. An incision is then made through the skin, over the spinous processes, extending from the occiput to the sacrum, and the muscles, fasciæ, etc., detached from the vertebræ so as to expose the laminæ on both sides. These are then sawed through, the saw being held parallel with the spinous processes, and the saw-cut made near where the laminæ join the pedicles. These are sawed through from the second vertebra to the sacrum and removed,

the chisel or bone-cutting forceps being used as aids if necessary. Inspect the meninges and remove these with the cord, carefully detaching, with a sharp knife, the nerve-roots as they pass out of the canal. The lower end of the cord, with its membranes, is first detached, and the removal continued from below upward. During the removal of the cord, whatever traction may be necessary should be made on the *meninges only*, and traction on, or crushing of, the cord should be carefully avoided. Lay open the meninges and examine the cord by making transverse incisions a centimeter apart.

The examination of the *joints* and *bones* of the skeleton may have preceded the visceral examination, but ordinarily it is deferred until that has been completed. Sometimes it is desirable to obtain bone-marrow without fracturing or otherwise

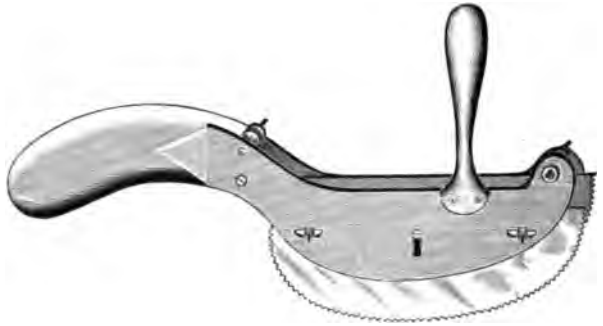

FIG. 22.—DOUBLE SAW FOR SAWING THROUGH THE LAMINÆ OF BOTH SIDES AT ONCE. It saves time and labor, but equally good work can be done without it.

severing the continuity of the bone. This is best accomplished by two saw-cuts parallel, one or two centimeters apart, and extending a little over half-way through the bone; by means of a chisel this block of bone is split out, bringing with it the marrow. A block of wood may be slipped into the space occupied by the piece of bone removed, and, where this fits tightly, bringing the tissues together over it will usually prevent the occurrence of a fracture during the ordinary handling of the body.

The removal of the salivary glands is not often demanded. The sublingual and submaxillary glands may ordinarily be removed by the method already described when considering the larynx and pharynx. A portion of the parotid gland can sometimes be removed by dissecting the skin down from the temporal region anteriorly, and below the incision already advised for exposing the skull.

In order to make a bacteriologic examination, it will be necessary to have on hand a Bunsen burner, alcohol lamp, or other means of sterilizing the instruments used. Cover-glasses, cover-glass forceps, platinum wire, various culture media, and labels will be needed. In order to secure material not contaminated by accident, it will be necessary to enter all cavities through an aseptic field. The disinfection of the area is best accomplished by heat. In order to secure inoculations from the peritoneum, it will be necessary, as soon as the wound in the abdominal wall approaches the cavity, to sear the surface with a hot scalpel, or, what is better, a spatula; this must be done thoroughly; through this seared surface, with instruments kept sterile by frequent passage through the flame, the wound is cautiously extended until the cavity is reached. At once cover-glass spreads and inoculations are made. In a like manner the pleura may be opened through an intercostal space. Inoculations from the interior of the pericardium are best obtained by

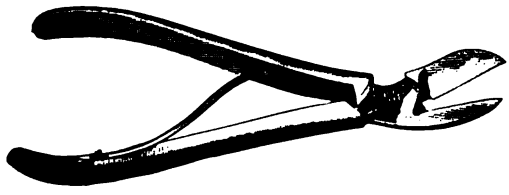

FIG. 23.—BONE-CUTTING FORCEPS.
These are not absolutely essential, but will be convenient. They should be long—not less than fifteen centimeters.

cautiously searing the fold raised as already directed (p. 28), and puncturing with a hot knife or scissors. To secure blood from the heart, a part of the surface is sterilized by searing with a hot iron, or one of the great vessels may be similarly treated and opened, using for this purpose a hot knife or scissors. A platinum loop may then be thrust into the cavity, and inoculations and spreads made in the usual manner.

In considering organs a definite field or plan should be adopted. Of course, this will be quite often varied, but it has the advantage of occupying no more time than any other method, and assures a systematic record which makes all postmortems comparable. The following is advised, although each worker will probably acquire a routine of his own: (1) *Malposition*, and, if out of place, is the malposition congenital or acquired, and what influence has it had on the position or function of other organs: *e. g.*, a misplaced right kidney may press upon the

duodenum or bile-duct or upon both. After removal it is too late to determine such facts, which may be of the highest importance in explaining symptoms. (2) *Malformations.* (3) *Make measurements* of the organ and *weigh* it; as the organ can be weighed only after removal, and as the removal severs its connection with the body, note must be made of *color*, *consistency*, *density*, and *shape*,—the latter being outlined when the measurements are made,—and a full *description of its external appearance* must be given; at the time of severing its attachments the *fullness of the blood-vessels*, the presence or absence of *edema*, and, if it possesses a duct, the condition and contents of that structure, must all be recorded. Whatever observations are to be made with regard to the ducts of organs must be completed before severing their connections. These studies enable one, to a certain extent, to record the presence or absence of the following points, which come next in order: (4) *Atrophy*, including hypoplasia or aplasia. (5) *Hypertrophy*, including *hyperplasia.* (6) *Infiltration.* (7) *Degeneration.* (8) *Inflammations*, including acute *infections.* (9) *Lesions of systems:* (*a*) *vascular;* (*b*) *lymphatic;* (*c*) *nervous.* (10) *Chronic infections.* (11) *Tumors.* (12) *Parasites.* If the steps indicated be followed, but little will be overlooked.

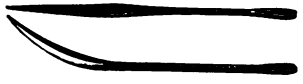

FIG. 24.—POSTMORTEM NEEDLES. These should be eight to fifteen centimeters long and correspondingly heavy.

As soon as an organ is incised pieces should be removed and fixed for microscopic study; the records may be completed after the microscopic examination is finished.

PRESERVATION OF TISSUES.

For preserving gross specimens alcohol is most commonly used. The tissue is washed in running water for a few hours to remove adhering blood, and is then placed in fifty per cent. alcohol; at the end of from two to four weeks the alcohol should be replaced by sixty per cent. alcohol, in which the tissue may be preserved indefinitely. If a snowy whiteness is desired, a mixture of glycerin one part, water three parts, and alcohol five parts will be found useful for the final preservative. Specimens that have been preserved in glycerin mixtures are of little value for microscopic purposes, as they can be frozen, embedded, or infiltrated only with the greatest care, and usually with unsatisfactory results. Of late, formalin * has come into great demand for the

* Formalin is a proprietary article; a forty per cent. aqueous solution of formal-

hardening and preservation of tissues. A ten per cent. solution in water will be found convenient, or the following when more time is available: The specimen to be preserved is lightly washed in water only, to remove adhering blood. It is then placed for ninety-six hours in—

Formalin,	250 c.c.
Nitrate of potassium,	10 gm.
Acetate of potassium,	30 gm.
Water,	1 liter.

Wash thoroughly in water and place in eighty per cent. alcohol for twenty-four hours, and permanently preserve in a mixture composed of acetate of potassium one part, alcohol sixteen parts, and glycerin two parts. This mixture preserves the color fairly well, and after a time the specimen can be handled without injury to the hands.

The following solution may be substituted for the final preserving mixture containing alcohol:

Acetate of potassium,	200 gm.
Glycerin,	400 c.c.
Water,	2000 c.c.

Fixation is accomplished in the formalin solution and is followed by placing the tissue in eighty per cent. alcohol for twenty-four hours, then in ninety-five per cent. alcohol for twenty-four hours, and by final preservation in the mixture of acetate of potassium, glycerin, and water. Exposure to the light for any great length of time causes the colors to fade. After considerable fading partial restoration may be brought about by immersion in amylic alcohol.

Organs or specimens not too large (one kilo) can be preserved in formalin vapor by placing the material to be preserved on a bed of cotton in an air-tight jar, previously moistening the cotton with pure formalin, and for the first few days keeping the specimen covered by filter-paper moistened with formalin.

For hardening brain-tissue, formalin has largely superseded Müller's fluid * for the gross specimen, and for certain purposes affords a satisfactory fixation for histologic research. Müller's fluid darkens the tissues, and thus alters their macroscopic appearance.

Small cysts, such as those of the echinococcus, are best preserved in a ten per cent. solution of chloral in water.

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dehyd gas, dissolved in water. The original formalin was expensive, but equally efficient solutions, under other names,—as *formalose*, *formol*,—can be obtained now at a price making preservation by this method cheaper than with alcohol.

* For formula of Müller's fluid see next section, p. 49.

CHAPTER II.

HISTOLOGIC METHODS.*

Morbid Histology.—*Technic.*—Sections of the fresh tissue may be cut either free-hand or by means of Valentine's knife, which consists of two parallel knife-blades of the utmost sharpness, separated from each other by a small aperture just as wide as the section is to be thick. Both methods are unsatisfactory, and are rarely used. Fresh tissue may be cut by freezing, as will be directed later. Since the publication of the first edition of this book, extended experience has convinced me of the necessity of thoroughly fixing all tissues before attempting to section them. By *killing* or *fixing* is meant the destruction of all metabolic processes and the securing of the tissue permanently in just such a condition as it presented during life, retaining the cell pictures as perfectly as possible. The following methods are advised:

(*a*) Chromo-aceto-osmic acid mixture (Flemming's solution). For this solution keep on hand the following stock solutions, and make up for use as wanted, in the proportion given:

Stock solutions to be kept on hand.	*Quantity needed to make up Flemming's solution.*
1 per cent. aqueous solution of chromic acid,	25 volumes.
1 " " " " osmic "	10 "
1 " " " " acetic "	10 "
Water,	55 "

All the water used in making the stock solutions or the final mixture must be distilled, and all containers should be chemically clean and dust free.

Fixation of small pieces will be complete in from one-half to

* In the present edition of this book there have been inserted, whenever their importance seemed to demand it, such technical directions as may be necessary for the demonstration of special reactions or methods. When searching for directions bearing on some point, the student is advised to consult the index. No attempt can be made in such a work as this to go into the subject of histologic technic with elaborate detail. A few methods can be taught, it is believed, thoroughly; but for further detail as to special methods the student had best familiarize himself with that best of all books for the worker with the microscope, "The Microtomist's Vade-mecum," by Arthur Bolles Lee.

two hours, although a longer time may do no injury. A period beyond a few hours, however, is likely to make the tissues brittle. After fixing, wash thoroughly in water. This is best accomplished by washing in flowing water for at least six hours. Proceed to embed at once or preserve in seventy per cent. alcohol until needed.

(*b*) Platino-aceto-osmic mixture (Hermann). Like the foregoing, it is best freshly prepared:

Stock solutions to be kept on hand.	*Quantity needed to make up above solution.*
1 per cent. aqueous solution of platinic chlorid, . . .	15 volumes.
2 " " " osmic acid, ...	2 "
Glacial acetic acid, ...	1 volume.

This solution is used as already directed for Flemming's solution, and should be followed by the same careful washing. Tissue so prepared may be treated as already directed for tissue prepared in Flemming's solution.

(*c*) The most useful fixing agent for general use is corrosive sublimate. The solution keeps well and fixes thoroughly, although for pure cell study the foregoing solutions are probably better. The solution is prepared by dissolving 125 gm. of corrosive sublimate in a liter of 0.5 per cent. solution of sodium chlorid in water. The solution of the corrosive sublimate being effected in the boiling salt solution, on cooling crystals of corrosive sublimate are thrown down, but are again taken up as the solution is used over. Small pieces of tissue fix in this solution in from one-half to two hours. The used solution is filtered back into the stock solution, and the tissue washed in water or, what is better, seventy per cent. alcohol. A little experience soon enables one to infer when the stock solution has become exhausted. By reason of its convenience, keeping qualities, cheapness, and the simplicity of the technic, it is most used.

In fixing by any of the above methods, the tissue should be in small pieces, not larger than 0.5 to 1 cm. cube. The quantity of the fluid used should be abundant, and exceed several times the volume of the tissue to be fixed.

For the preparation of tissue containing nerves, or the central nervous system, nothing has been more generally used than bichromate of potassium. It is used in two to five per cent. aqueous solutions, Müller's fluid, or Erlicki's solution:

Müller's Fluid.		*Erlicki's Solution.*	
Bichromate of potassium, .	2 parts.	Bichromate of potassium, .	2.5 parts.
Sulphate of sodium, . . .	1 part.	Sulphate of copper, . . .	1.0 part.
Water, ...	100 parts.	Water, ...	100.0 parts.

The latter hardens much more rapidly; a spinal cord may be hardened in two weeks by this mixture, while by Müller's fluid as many months would be necessary. As the penetration of neither of the above is rapid, nerve tissue placed in them should be freely incised to aid penetration, a spinal cord being cut transversely every centimeter. As soon as the fluid becomes dark or cloudy it should be changed, and the quantity should always be several times the bulk of the tissue. After hardening is completed, the tissue should be thoroughly washed in water before transferring to alcohol.

The foregoing bichromate solutions have been largely supplanted by two more recent acquisitions:

Zenker's Fluid.

Bichromate of potassium,	2.5 parts.
Sulphate of sodium,	1 part.
Corrosive sublimate,	5 parts.
Water, enough to make	95 "
Glacial acetic acid, to be added just before using,	5 "

Fix small blocks of tissue, 0.5 centimeter in thickness, for from one hour to twenty-four hours; wash in running water for twelve hours and preserve in eighty per cent. alcohol.

Orth's Fluid.

Müller's fluid,	100 parts.
Formaldehyd (forty per cent. solution),	10 "

The fluid should be freshly prepared from the two stock solutions. The material should be small pieces—cubes from 0.5 to 1 cm. Fixation will ordinarily be complete in from two to four days; the material should then be washed in running water for from six to twelve hours and preserved in eighty per cent. alcohol.

Alcohol is sometimes used as a fixative. To be efficient it must be as nearly absolute as possible. Weaker solutions give rise to easily recognized and quite characteristic artifacts. For the demonstration of bacteria in tissue, fixation by alcohol is permissible; it has, however, no advantages over corrosive sublimate, even for this purpose, and is always associated with a very grave disadvantage, in that one desiring to study the nuclei may find that the fixative has not properly preserved them.

Alcohol is largely used as a dehydrating agent and for the preservation of tissues during the interval between fixation and the final steps in the embedding process. It is the ideal agent for neither purpose, but for the present it seems to be the best that we possess.

SECTION CUTTING.

INFILTRATION METHODS.

1. **Paraffin.**—After fixing and washing as already directed, the tissue to be infiltrated is dehydrated by passing through alcohols of increasing strength—seventy per cent., twenty-four hours; eighty per cent., twenty-four hours; ninety per cent., twenty-four hours; absolute, twenty-four hours. As alcohol does not mix with paraffin, it must be displaced by some agent that will dissolve paraffin. For this purpose numerous reagents have been used, such as chloroform, turpentine, xylol, toluol, benzol, cedar oil, and many allied bodies. Many of these alter the tissues; probably all of them do slightly, but the least objectionable is cedar oil. From absolute alcohol the tissue is carried into the clearing agent, preferably cedar oil, and, to make the

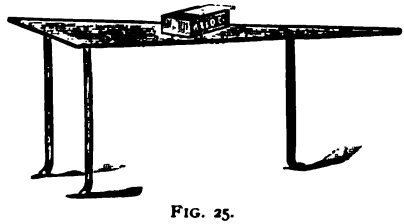

FIG. 25.

Flat-iron-shaped copper table, which may be used for paraffin infiltration as well as for the fixation of blood films. If a Bunsen burner be placed under the tip of the sharpest corner, to the right of the single leg, and the strip be heated to a constant temperature, so that the extreme end from the burner may be cold, any degree of temperature between the cooler part and that part over the burner, which is practically red-hot, may be obtained. As shown in the cut, a small paraffin dish is placed over a spot where the paraffin is kept barely melted.

change gradual, the cedar oil is diluted with an equal part of absolute alcohol; after twenty-four hours' treatment in this mixture the tissue is transferred to pure cedar oil for twenty-four hours, and then to paraffin, which in summer has a melting-point of 50° C., in winter of 45° C. The paraffin must be kept as near the melting-point as possible by means of a paraffin oven and a thermoregulator. After twenty-four hours the tissue is transferred to fresh paraffin at the same temperature, in which it is kept from twelve to twenty-four hours. The gentle heat, continuously applied, displaces the cedar oil and permits the paraffin to infiltrate the interstices of the tissues. A wooden block—about a two-centimeter cube—has one end warmed over a Bunsen burner and dipped in the melted paraffin. It is then wrapped with a strip of paper four centimeters wide, so that the paper projecting from the end of the block that has been warmed and coated with

paraffin forms a well as deep as the tissue to be mounted. The block of tissue is then placed in position at the bottom of the well, arranged to cut to the best advantage, and melted paraffin

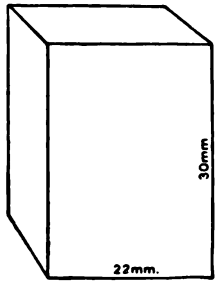

FIG. 26.
Block of hard wood or of rubber fiber as usually received in the laboratory.

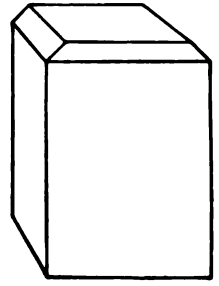

FIG. 27.
Same block as figure 26, with corners properly trimmed to receive paraffin or celloidin for embedding.

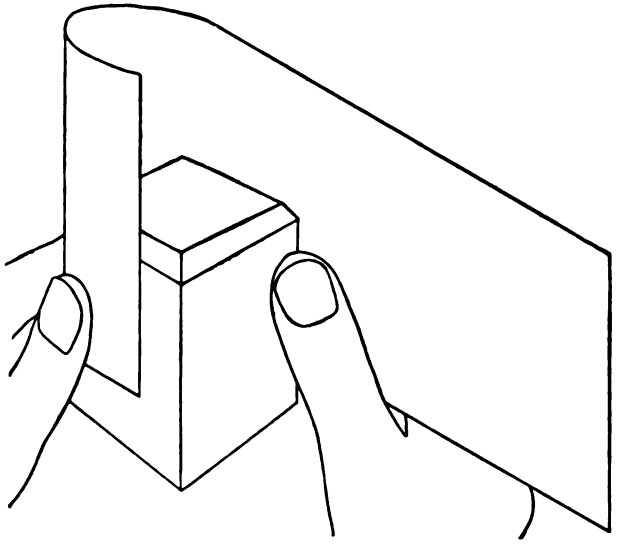

FIG. 28.
Method of applying paper to block.

is poured in until the well is filled. This is allowed to cool and the paper is then removed. The paraffin is now gray, appears granular, and is said to be in the crystalline form; if put in a warm place,—care being taken that it is not warm enough to

melt the paraffin,—it soon becomes transparent, or, it is said, the paraffin becomes amorphous or hyaline.

The block is now ready to cut. It is trimmed down nearly to the tissue, each side being cut so as to present a surface square to the knife, the general aspect of the block being that of a truncated pyramid. The paraffin trimmed off is remelted, and may be used many times. The block is clamped in the holder of the microtome so that the cutting-edge of the knife strikes squarely against the block along its whole length; the knife is so arranged that it cuts like a chisel, and not with a drawing motion. To get the best sections, the paraffin must be of the

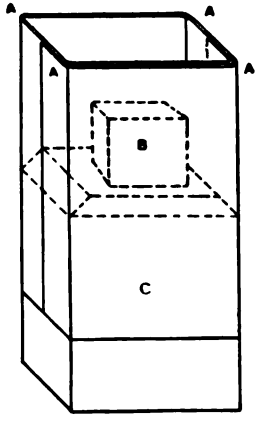

FIG. 29.

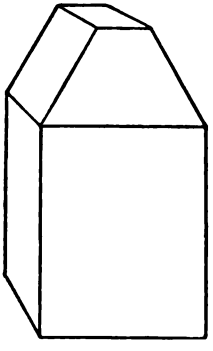

FIG. 30.

Paper (A, A, A, A) properly wrapped around block (C), with block of tissue (B) to be embedded, ready for pouring the paraffin in and completing the cast. After the cast cools (see text) the paper is removed and the paraffin is trimmed, as shown in figure 30, carefully avoiding the block of tissue, which should be thoroughly covered by the paraffin at all points.

proper temperature, as this determines the density; in summer the block may have to be cooled by ice; in winter it may require warming.

The most important factor in paraffin infiltration is thorough dehydration and clearing. Absolute or approximately absolute dehydration is necessary in order to secure penetration of the clearing agent—cedar oil, xylol, or whatever it may be. If the pieces of tissue are small, the stages of the process may be shortened. Tissue kept too long in strong alcohol or in the clearing agent or paraffin (warm) not infrequently becomes brittle. The occurrence of this condition should lead the worker to shorten the stages sufficiently to overcome the difficulty. When

osmic acid methods have been used for the purpose of determining the presence of fat, the clearing agent and paraffin may, under some conditions, partly remove the fat. In osmic acid preparations, when the fat is to be retained, celloidin infiltration is to be preferred.

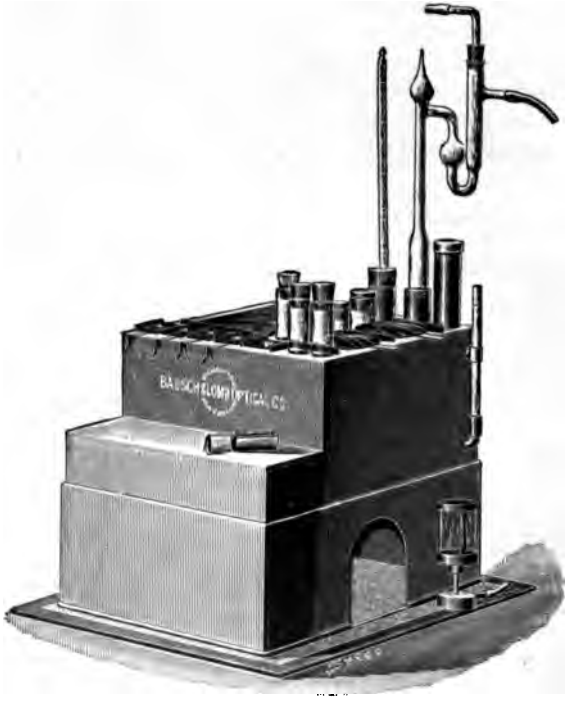

FIG. 31.—NAPLE'S PARAFFIN BATH FOR INFILTRATING TISSUES IN PARAFFIN.
The apparatus consists essentially of a series of receptacles for holding the melted paraffin, with a surrounding water-bath retained at an even temperature by a thermoregulator.

FIG. 32.—FORCEPS CONVENIENT FOR HANDLING COVER-GLASSES, BLOCKS OF TISSUES, AND SECTIONS.

It will be seen that the foregoing process requires days, and to overcome this objection Reeves has recommended the following: (1) Fix in saturated alcoholic solution of corrosive sublimate for one hour. By this method fixation and dehydration go on together; (2) absolute alcohol, one hour; (3) xylol, one

FIG. 33.—LABORATORY MICROTOME.

Can be used, as shown in the cut, for celloidin sections; an attachment for freezing may be substituted for the clamp shown in the illustration immediately below the knife. For paraffin blocks the knife must be turned with its cutting-edge at a right angle to the plane of the knife-carrier.

hour. As xylol has a very low volatilizing point, it quickly evaporates in the paraffin bath, and permits the rapid penetration of the paraffin; it is kept one hour in the first paraffin and one hour in the second, when it is cast. In order to prevent the crystallization of the paraffin the cast is plunged into ice-water as soon as its surface has cooled sufficiently to form a thin film; the cooling may be facilitated by holding the block out of the window in winter or by gently blowing upon it in summer. The cast is now trimmed and cut. Of course, the pieces of tissue to be prepared in this way must be very small,—not over 0.5 cm. cube,—and the results can not be considered as comparable to the slower method already described.

Mounting Paraffin Sections.—If the sections be properly cut and the infiltration has been satisfactory, they will adhere in chains or ribbons as they come away, or each section may be removed from the knife as rapidly as cut, using a short sable

FIG. 34.—SMALL MICROSCOPIC SCISSORS.
Suitable for trimming sections and labels and for other microscopic work.

brush for the purpose. To insure thin sections, the knife must be of the utmost sharpness. Before the sections are cut it is best to prepare the slips to receive them. The slips or slides are thoroughly cleansed with alcohol and dried, using toilet-paper or a soft cloth for that purpose. Place on the center of the slide a very small quantity—less than a drop—of Mayer's albumin, and with a perfectly clean finger wipe it off. This leaves an almost imperceptible layer of the albumin. On this place a few drops of water,—enough to float the section just clear of the albumin,—and place the section on the water; gently warm the slide, being careful not to melt the paraffin; as the section becomes warm it will straighten out, all folds and wrinkles disappearing. Now carefully pour off the excess of water, and the section falls upon the layer of albumin, to which it adheres. Mayer's albumin is composed of egg-albumen (white of egg) and glycerin, of each 100 c.c., to which one gram of salicylate of sodium has been added to aid the glycerin in preserving the

albumin ; after thoroughly mixing, the mass is filtered through paper—a process requiring weeks. The albumin fixes the section to the slide, so that it may be taken through the subsequent

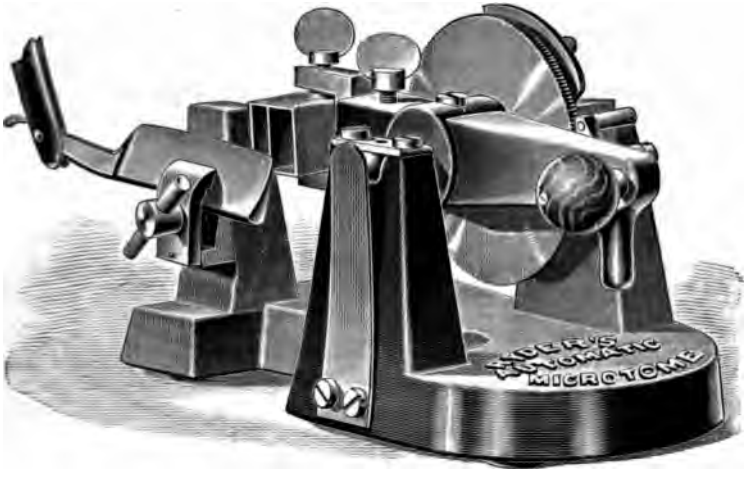

FIG. 35.—RYDER MICROTOME.

Expressly adapted for paraffin sections and for cutting in series; can not be used for frozen sections. Can be used for celloidin if the chloroform method of hardening has been adopted.

FIG. 36.—RANVIER'S MICROTOME.

Blocks of tissue infiltrated with celloidin or paraffin may be cut in sections free-hand with an ordinary razor; better results may be obtained by even so simple a microtome as the above (Ranvier's microtome), or very much better results by the Ryder, Minot, or Bausch and Lomb instruments.—(*Illustration from Gould's Dictionary.*)

processes without the least trouble. After the section has been drained of the water upon which it was floated to facilitate

straightening out, it is placed in a drying oven to get rid of any remaining water. In ordinary work where no great haste is demanded the slide may be placed in some warm place, protected from the dust, until perfectly dry. After drying, which may require from four to twenty-four hours, the slide is gently warmed until the paraffin just melts, and no more; it is then thrust into ordinary

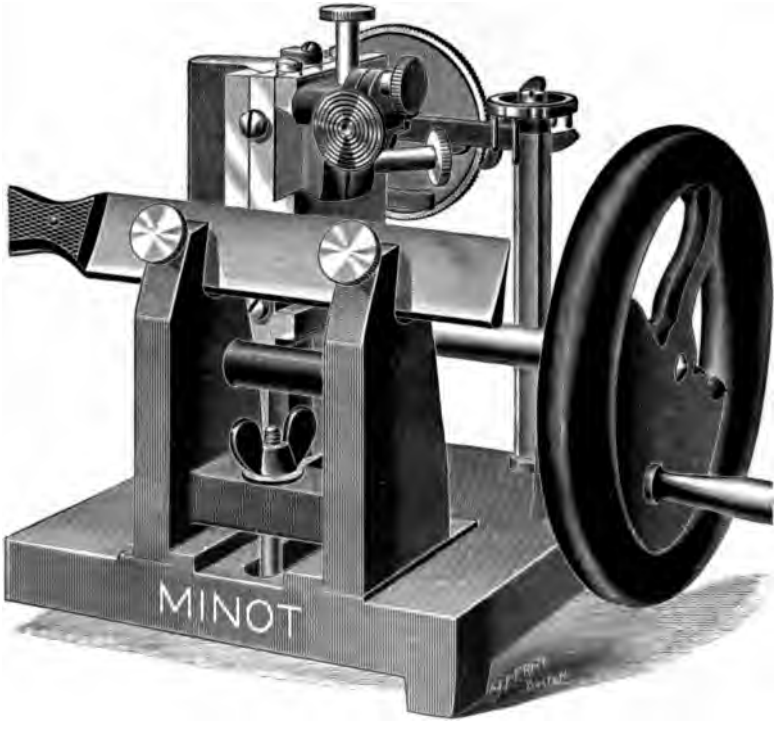

FIG. 37.—MINOT MICROTOME.

Two sizes of the instrument are made: the illustration is of the smaller size. The corrugated metal plate just above the knife is intended to receive the block of tissue which is cemented on by the use of melted paraffin. The writer has found this extremely difficult and tedious, and has devised a clamp which replaces the complicated orienting attachments shown in the cut, and grasps the block shown in figure 30, without the necessity of cementing the tissue to the microtome.

kerosene, or, what is slightly better but much more expensive, xylol; either of these quickly removes the paraffin, usually requiring about fifteen minutes; wipe off the excess of xylol, rinse the slide in alcohol, and place the slide in that liquid until the xylol is removed. From the alcohol the section is stained as will be directed later. If the tissue was fixed in corrosive

sublimate, this must be removed by treating the section with tincture of iodin, in which it is immersed for fifteen minutes; it is then washed with a few drops of alcohol and placed in a jar of alcohol, from which it is removed for staining when desired.

2. Celloidin Infiltration.—Celloidin is a proprietary product first used in wet plates for photography, and is nothing more than a nonexplosive gun-cotton. As used, it is dissolved in equal

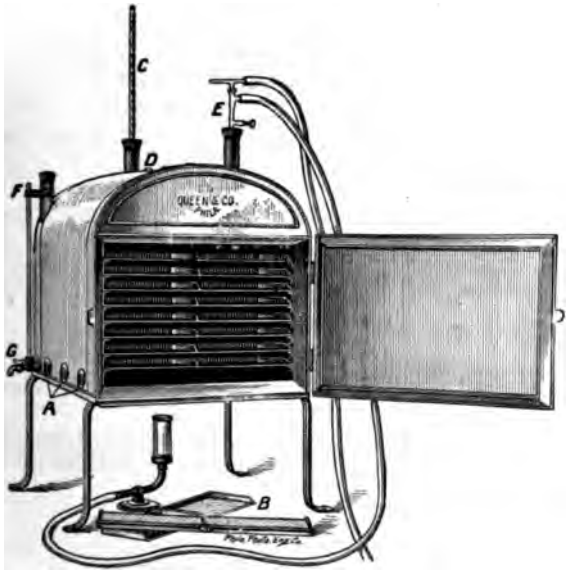

FIG. 38.—DRYING OVEN.

A. Three tubes for admitting air to interior. At *D* are three similar exit tubes. *B*. Shelves upon which slides are placed at the student's desk, from which, after labeling each slide and placing under the slides a piece of paper with his name and desk number, he places the tray in the oven. *C*. Thermometer. *E*. Thermoregulator. *F* Water-gage. *G*. Cock for emptying the water space. The temperature of the oven should never reach the melting-point of the paraffin, and had best be between 37° C. and 40° C.

parts of alcohol and ether, thus making a collodion that, so far as the author can observe, has no advantage over a good collodion made from gun-cotton. The alcohol used for this purpose should be absolute; the solution will be facilitated by placing the celloidin in a tightly stoppered bottle—a citrate of magnesia bottle is to be recommended—and pouring on the absolute alcohol, which should be allowed to remain in contact with the celloidin for twenty-four hours, when an equal volume of ether should be added. By this method solution will be complete and no time will be lost. As ordinarily used, two solutions are needed—

one a thick, syrupy solution, and a second thin solution made by diluting the thick solution with an equal quantity of alcohol and ether. The tissue to be infiltrated is fixed and dehydrated as already described for paraffin ; it is then placed for twenty-four hours in a mixture of equal parts of alcohol and ether. From this the tissue is transferred to the thin solution of celloidin. The best results are obtained by leaving the mass for infiltration several days in this solution, when it is placed for an equal length of time in the thick solution. A block is then soaked in alcohol and ether for one or two hours or longer, and one end is coated with celloidin and wrapped in paper, as already directed for paraffin. Into the well the infiltrated piece of tissue is placed, arranged as desired for cutting, and the thick celloidin solution is poured over it ; the mass, which is now said

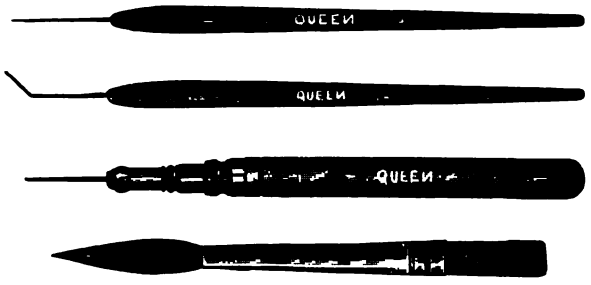

FIG. 39.—NEEDLES AND BRUSH SUITABLE FOR HANDLING SECTIONS.

to be cast, is placed under a lightly fitting bell-jar or cover until the celloidin begins to set, when it is thrown into eighty per cent. alcohol for hardening. At the end of twenty-four hours it will be found sufficiently hard for cutting, but it may be kept indefinitely in the alcohol and cut when desired. Unlike paraffin, celloidin must be cut with the microtome knife at an angle to the block,—that is, with a drawing motion,—and, while the paraffin was cut with a perfectly dry knife, the celloidin must be cut with a knife kept flooded with eighty per cent. alcohol. Each section is removed from the knife as cut and is transferred to eighty per cent. alcohol, in which it may be preserved until wanted for use. The great advantage claimed for celloidin is that, unlike paraffin, it need not be dissolved out before the section is stained. Stains such as carmin and hematoxylin may be used, the celloidin holding the sections together during the manipulations incident to staining.

Gilson's Method.—A satisfactory method of celloidin infiltration is that devised by Gilson, in which, after dehydration and treating with the alcohol and ether mixture, the tissue is placed in a test-tube containing several centimeters of thin celloidin solution; after a few days in the thin celloidin, the test-tube is immersed in a water- or paraffin bath at about 42° C., at which temperature the solvents (alcohol and ether) rapidly evaporate, thereby hastening penetration and increasing the density of the infiltrating mass. When the solution has evaporated to about one-third its original bulk, it is turned out and cast as in the slow process. The hardening of the block is greatly facilitated and the results are improved by hardening in chloro-

FIG. 40.—DISH FOR REMOVING PARAFFIN AND CORROSIVE SUBLIMATE AND FOR DEHYDRATING.

May also be used for staining, and for the same purposes as the Stender dish. After the sections are cemented on the slide the slides are placed back to back and slipped down in the groove, as shown at B at the bottom of the dish. If the slides are thin, the dish will hold ten at one time.

form. The process is applicable to blocks that have been infiltrated either by the slow or by the rapid method.

As soon as possible after the cast is made the mass is placed in a desiccator or sieve dish, or in a bottle containing a teaspoonful of chloroform and having a tightly fitting stopper. A support is arranged above the chloroform, on which the block to be hardened is placed, and the vessel is then tightly closed. From two to twelve hours will be sufficient for the hardening, after which the block is placed in a mixture of cedar oil two parts and chloroform one part; more cedar oil is added from time to time until nearly pure cedar oil is attained. The sections are cut dry,

as in the paraffin method. The block may be preserved indefinitely in the cedar oil.* After cutting, the sections are washed in alcohol in order to remove the cedar oil, and may then be stained.

Sections obtained by the celloidin embedding and infiltration process may be secured to the slide by ether vapor or by a very thin layer of celloidin. The best method is to float the section on to the slide, blotting it carefully with bibulous paper, and, from a bottle containing a small quantity of ether, to pour the vapor of the ether upon the section. This will sufficiently soften the celloidin to make it adhere to the slide during the rest of the manipulations. It is to be remembered that celloidin sections must be kept moist throughout the entire course of their preparation. Drying them is, as a rule, injurious, if not destructive.

3. Congelation Method.—Fresh tissue may be frozen and sectioned, but the best method is that of Hamilton: (1) Harden; (2) wash out the hardening fluid; (3) place in sugar solution for from two to twenty-four hours; this solution is composed of two ounces of sugar dissolved in one fluidounce of water; after removing from the syrup, wash lightly in water and (4) place in mucilage for two hours. The tissue may now be put on the drum of the freezing microtome, frozen, and cut. Remove sections from the knife with a soft brush, and wash them thoroughly in water to remove the gum and sugar; the staining is proceeded with as for other sections.

Remarks on the Foregoing Processes.—For small pieces of tissue the paraffin method is best; thinner sections can be cut, and the method of cementing them on the slide makes the handling most convenient. For large blocks, such as an eye, and for tissues from the brain, spinal cord, or larger nerve-trunks, celloidin is to be preferred. After using the freezing method to a very large extent for about ten years, the author is thoroughly convinced that it is not to be relied upon. The ice crystals that form in freshly frozen tissue break up the cells and give results that may mislead the most experienced investigator. The distortion of structure incident to the use of congelation masses, their macerating properties, and the difficulty in removing the infiltrate, have led me to give them up entirely for laboratory work; only the crudest kind of pathologic work can be performed by

* Since the publication of the last edition of this manual the writer has known of considerable difficulty by reason of the softening of the celloidin when preserved in cedar oil. The cause of this unfortunate complication was not at first discovered. It would appear that the success of the method depends upon the quality of the cedar oil. Mayer has recently informed Harris that cedar oil prepared by Schimmel did not in the least soften the celloidin.

the freezing and congelation methods at present at our disposal, and the results are always open to criticism.

STAINING AND MOUNTING.

General Remarks.—As a rule, it is best for the student to work with one stain until he is familiar with it; and before combining two or more stains it is best for him to familiarize himself with the action of each stain when used alone. The student should remember that there are two principles involved in staining: (1) When a stain shows unusual selectivity in certain bodies, such as cell nuclei, it is allowed to act only long enough to color the desired bodies; its action is then stopped and the preparation of the mount continued. (2) The stain is permitted to act until everything that will receive the color is stained, and then some agent is applied that differentiates certain elements by removing the stain from other structures. Thus, acid alcohol is used to differentiate in carmin staining, and water after hematoxylin. Alcohol or water, either of which may be used with or without acidulation, are also used to differentiate with the anilin dyes. The objection to examining sections unstained is that no one structure is prominent; and if everything in the section be uniformly colored, nothing is gained by the staining. For this reason differentiation is more or less applicable to all stains. After differentiation, or in some instances simultaneously with this process, dehydration is necessary in order to proceed with the next step—clearing the section. The process of clearing is necessary in order to examine the section by transmitted light. Clearing also makes the application of a permanent medium, such as xylol balsam, possible.

The clearing agents mentioned in the preceding and following pages are not all applicable under all circumstances. The best clearing agents are cedar oil, creasote, xylol, and possibly one or two other agents having more or less special uses.

Carmin and Hematoxylin.—The two stains most frequently used in laboratory work are carmin and hematoxylin. Strongly alkaline stains, such as lithium carmin, are no longer to be commended; the same is true of bulk staining. The *carmin* most useful in the laboratory is Grenacher's alcoholic borax-carmin:

Alcoholic Borax-carmin.

Carmin (best No. 40), ... 3 parts.
Borax, ... 4 "

Mix and pulverize thoroughly in a mortar, and add 100 parts of water; boil for half an hour; add an equal bulk of seventy per cent. alcohol; set aside for one week, and then filter.

To stain, add enough of the stain to the section on the slide abundantly to cover it, and allow it to act for from five to ten minutes or longer. Drain off the excess of stain, wipe around the section with paper or soft cloth, and apply acid alcohol.

Acid Alcohol.

Hydrochloric acid,	1 part.
Water,	29 parts.
Alcohol,	70 "

The section, as soon as the acid alcohol is applied, turns from a purplish-red to a light crimson, and becomes more nearly transparent; it is then washed in strong alcohol, the excess wiped from around the section, and the latter is covered with creasote. The alcohol dehydrates and removes the acid, which is the differentiating agent, and the creasote renders the section clear for examination by transmitted light. As soon as the section is clear remove the excess of creasote, apply a drop of balsam, and cover with a thoroughly cleansed cover-glass; label the section. It will now keep indefinitely.

One of the best carmin stains is *Mayer's carmalum.* This is made by dissolving 1 gm. of carminic acid and 10 gm. of alum in 200 c.c. of distilled water, using heat if necessary. In order to preserve the solution add 0.1 per cent. of salicylic acid, or 0.5 per cent. of salicylate of sodium. The solution is clarified by decanting or, better, by filtration. The great advantage of this solution lies in the fact that it is almost impossible to overstain with it, and by careful washing and differentiation practically all intermediate degrees of staining can be obtained. It may be differentiated in acid alcohol, as already directed for borax-carmin, or, if the alcohol used for the subsequent dehydration be strongly tinted by the addition of picric acid, the combined action of the two stains (the carmin being a nuclear stain and the picric acid a protoplasmic stain) will afford one of the best general stains found in the laboratory. Picric acid may be used in the same way with borax-carmin, but the result is not so satisfactory.

Hematoxylin Staining.—One of the best forms of this stain is Delafield's, made as follows: Dissolve 4 gm. of hematoxylin crystals in 25 c.c. of strong alcohol; add this solution to 400 c.c. of a cold, filtered, saturated aqueous solution of ammonia alum; expose to light and air for several days. Filter and add:

Glycerin,	100 c.c.
Methylic alcohol,	100 c.c.

Allowed to stand in the light, with the bottle loosely corked, this mixture turns dark purple, almost black; it should then be filtered and kept in tightly stoppered bottles. For use it should be much diluted; the amount of dilution must be determined for each lot, varying with the degree of oxidation and with the age of the stain. If made with distilled water, and provided that all vessels and containers are kept chemically clean, this stain will keep for years. To use it, the sections on the slide, prepared as already directed, are covered with the diluted stain for from five to fifteen minutes, washed with water, dehydrated in alcohol, cleared with creasote, and mounted in balsam as directed in the last steps for carmin, except that differentiation is secured by the use of water, and not by acid alcohol. A better stain is secured

FIG. 41.—DROPPING-BOTTLE WITH BARNES' DROPPER, WHICH CLOSES THE MOUTH OF THE BOTTLE LIKE A RUBBER STOPPER.

These bottles are usually of one ounce capacity, and are convenient for holding stains and staining reagents.

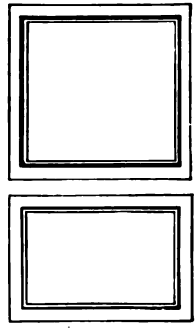

FIG. 42.—PROPER SIZE LABELS FOR LABELING MICROSCOPIC SLIDES.

by taking enough distilled water in a bottle or staining dish to immerse the slide on end; to this add enough of the hematoxylin to just a little more than color the water; the sections cemented on the slide are left in this overnight (or even for twenty-four hours), washed in water, and treated as previously directed. Hematoxylin not only stains the nucleus, but affords a light tint to the protoplasm as well. This latter, however, can be better secured by using eosin. After the section is stained in hematoxylin and washed in water, the excess of the water is removed and the section is treated for a moment in an alcoholic solution of *eosin* (0.5 per cent.), followed by alcohol and creasote, and is then mounted in balsam. The nuclei are stained purple by the hematoxylin and the cell protoplasm pinkish by

the eosin. This makes a very fair contrast stain, and brings out some pathologic bodies not shown by the hematoxylin. In addition, it shows red blood-corpuscles to the very best advantage, being a specific stain for hemoglobin. *Picric acid* may be used with hematoxylin to advantage, particularly if the sections are a little thick or if they are overstained in the hematoxylin. After washing the hematoxylin stain thoroughly in distilled water, the subsequent dehydration is accomplished by the use of alcohol containing a trace of picric acid. The nuclear stains obtained by this method are sharp, and the yellowish protoplasmic tints are beautifully transparent.

Anilin Dyes.—In addition to the use of these agents for staining bacteria, they have become important and useful adjuvants in certain microchemic reactions, which will be referred to under special headings throughout the book; and also for general stains. For practical purposes the anilin dyes may be divided into two groups:

1. *Basic group*, in which the staining property is due to the base present in the compound.

2. *Acid group*, in which the staining property is due to the acid principle.

The basic colors are, as a rule, sharp nuclear stains, while the acid dyes stain, more or less diffusely, the protoplasm in the cell. As a rule, the dyes are used as concentrated solutions (1) in water; (2) in five per cent. carbolized water; (3) in thirty to sixty per cent. alcohol, preferably about fifty per cent. Under some conditions the dyes seem to act best if the solutions are rendered faintly alkaline; or at other times, faintly acid. The alkalinity is usually secured by the addition of a very small quantity of carbonate of potassium, and the acidity by an extremely dilute solution of acetic, formic, or hydrochloric acid. The basic anilin dyes commonly used are safranin, fuchsin, methylene-blue, thionin, gentian-violet, toluidin-blue, etc. The acid stains mostly used are eosin, orange G, acid fuchsin, etc.

The following formulas and methods are introduced as examples, and after the student has familiarized himself with the technic given, he may apply the knowledge so obtained to staining with other and similar anilin dyes.*

* One of the great difficulties with anilin dyes is the inconstancy of their composition and the unreliability of many samples placed on sale. For this reason it is recommended that in purchasing the anilin dye the student should always specify the make of Grübler.

Safranin is a most excellent nuclear stain. The following formulas are to be recommended:

Saturated solution of safranin in water, heated to 75° C.; after thorough saturation, filter; stain from two to five minutes to twenty-four hours, depending upon the tissue, length of fixation, etc.; wash in water, differentiate and dehydrate simultaneously in alcohol, clear in xylol, and mount in xylol balsam. A mixture compared of one part of the above solution of safranin and one part of a saturated alcoholic solution of alcohol-soluble safranin makes a satisfactory stain, and may be used in the same way.

Methyl-violet.—One or two per cent. solution in water. Stain from two to five minutes or longer, and treat in the same manner as already given for safranin.

Methylene-blue.—*Unna's alkaline methylene-blue solution:* *

Methylene-blue,	1 part.
Carbonate of potassium,	1 "
Water,	100 parts.

The stain should be diluted to one-tenth its strength when required for use. Stain from half an hour to several hours, rinse in water, differentiate and dehydrate in alcohol, clear in xylol, and mount in xylol balsam.

Toluidin-blue.—Make a one per cent. solution of the stain in a five per cent. solution of carbolic acid in water; stain from five to ten minutes to twenty-four hours, differentiate and dehydrate in alcohol, clear with cedar oil, and mount in xylol balsam.

Ziehl's Carbolfuchsin.—Rub up 1 gm. of powdered fuchsin with 10 c.c. of alcohol in a glass mortar; dissolve 5 gm. of crystalline carbolic acid in 100 c.c. of distilled water; mix the two solutions and the stain is ready for use. The stain may be prepared by the addition of 10 c.c. of a saturated alcoholic solution of fuchsin to 90 c.c. of a five per cent. aqueous solution of carbolic acid. Stain sections two to five minutes to several hours; differentiate and dehydrate in alcohol, clear in clove oil or xylol, and mount in xylol balsam.

As a rule, sharpness of nuclear stain is obtained by overstaining, followed by careful *differentiation*, which must be stopped at a certain time; the best results are obtainable after repeated experiments and many failures. Alcohol as a differentiating

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* This stain resembles, when diluted, Löffler's alkaline methylene-blue, the formula of which is as follows:

Saturated alcoholic solution of methylene-blue,	30 c.c.
Potassium hydrate (0.01 per cent. aqueous solution),	100 c.c.

May be used for staining tissues, but is more useful in bacteriologic staining.

agent does not give the best results, nor is the differentiation in alkaline or faintly acidulated water ideal. Two of the most satisfactory differentiating agents with which the writer is familiar are glycerin-ether and styrone.

The **glycerin-ether mixture** (Unna) is obtained from Grübler, and should be diluted at least one-half for use. Sections are stained rather deeply in Unna's alkaline methylene-blue solution or Unna's polychrome methylene-blue or in carbol-toluidin-blue, rinsed in water, and covered with the diluted glycerin-ether mixture. At first the dye comes out in clouds; later, differentiation progresses more slowly. The exact point at which to arrest the differentiation can be learned by experience only. In order to arrest the action of the glycerin-ether the excess is poured off, the section washed in alcohol, cleared in cedar oil, and mounted in balsam.

Styrone is a solid, camphor-like body at a low temperature; at the ordinary room-temperature it assumes a syrupy consistence. It is a differentiating agent that also acts as a clearing agent and is superior to other differentiating agents in that the tissues may be watched under the microscope, without a cover-glass, during the process of differentiation. In order to apply it, the section, stained as already advised for glycerin-ether, is hastily washed in water, followed by alcohol, and the styrone is at once applied. The styrone first applied becomes cloudy, deeply dyed, and is poured off; fresh styrone is added, and the slide is placed on the stage of the microscope. As soon as the differentiation has become satisfactory the styrone is washed off with cedar oil, the application of the latter agent being continued until all differentiation has ceased; the cedar oil is then removed and xylol balsam and cover-glass are applied. In clearing sections stained by basic anilin dyes, disaster commonly follows the application of creasote. Xylol is considerably better, but the best results are obtained by the use of cedar oil, which acts slowly and must be given time; gentle warming hastens the clearing, but is rarely necessary if the dehydration has been complete.

Eosin may be used with either of the nuclear stains previously given. It is particularly useful with the toluidin-blue. Eosin, either as a saturated solution in water of the form soluble in that medium, or saturated solution of eosin in alcohol, using the form soluble in that agent, may be used as contrast stains before or after the toluidin-blue or methylene-blue; as both of these agents are discharged by eosin solutions, it is possibly better to stain first with eosin, rinse in water, and apply the nuclear stain

afterward. If the eosin be used after the nuclear stain, it should not be allowed to act too long, otherwise the nuclear stain may be discharged. As eosin acts as a differentiating agent, when used after the nuclear stain, care and experience are necessary to secure the best results. After the use of eosin, dehydration in alcohol and clearing in cedar oil are recommended.

For the use of eosin as a contrast stain with hematoxylin, see page 65. For the use of picric acid for the same purpose and with carmin, see pages 64 and 66.

THE MICROSCOPE.

A Desirable Laboratory Microscope.—Figure 43 illustrates a stand useful in a pathologic laboratory. The horseshoe base gives solidity by its long arms and great weight. To this base is attached the upright, which supports the superstructure; the stand should be handled by this piece entirely, never grasping the parts above in moving the microscope, as such a procedure is likely to injure the adjustments. At the upper termination of the upright is the joint for inclining the microscope for convenience in working. Running to the front from this joint is the stage upon which the slide is placed for examination; clips are shown for retaining the slide in position. Beneath the stage are the substage mountings, consisting of diaphragms for lessening the light, condensers for increasing the rays' intensity, and a mirror for reflecting the light upward through the optic axis of the instrument. These parts are adjustable by lateral movement, by rack, pinion, and screw motion. Behind the inclination joint, and above the stage, what is known as the upright arm rises; at its upper part is placed the fine adjustment, worked by a milled thumb-screw. Passing off in front of this upright arm is the horizontal arm, to which is attached the coarse adjustment by rack and pinion moved by the milled heads shown at both sides. The tube carrying the optic parts is attached to the horizontal arm by the rack and pinion coarse adjustment. The tube is so made that it may be drawn out to a standard length. At the upper end of the tube is the eye-piece; at the lower end, the objective. In the laboratory instrument, when, for any reason, an oil-immersion objective may not be desired, two objectives (a $\frac{2}{3}$ of an inch and a $\frac{1}{4}$ or $\frac{1}{6}$ of an inch) are mounted on a double nose-piece, by means of which either objective may be brought into use. In bacteriologic examinations in which an oil-immersion lens is indispensable, three objectives are mounted on a triple nose-piece, as shown in the cut. (Fig. 43.) In nearly all cases

FIG. 43.—MICROSCOPE SUITABLE FOR GENERAL PATHOLOGIC AND BACTERIOLOGIC WORK.

As shown here, it is fitted with three objectives, a $\frac{3}{4}$ of an inch, $\frac{1}{4}$ of an inch, and $\frac{1}{12}$ of an inch mounted on a triple nose-piece. For bacteriologic work the $\frac{1}{12}$ of an inch oil-immersion objective is necessary, but for normal and pathologic histology only the $\frac{3}{4}$ of an inch and $\frac{1}{4}$ of an inch will be needed. The stand here figured is also fitted with an Abbe condenser, iris diaphragm, and blue-glass. (For method of using and for description of parts, see pages 69 and 71.)

the examination should *begin* with the lower power, followed, *if necessary*, by the higher power.

To Use the Microscope.—The instrument is placed in front and slightly to one side—usually the right side—of the observer, and tilted at the joint so as to afford a comfortable position for observation without craning the neck or stooping the shoulders. By daylight, northern light or light from white clouds is preferable; if the window is exposed to the direct rays of the sun, a piece of thin tissue-paper is pasted over the glass, or the glass may be frosted or painted; direct sunlight should never be used except for photomicrography. If an artificial light is to be used, the microscope is placed about thirty centimeters from the light, and to one side, so that neither the heat nor the direct rays from the light will be thrown in the face or eyes of the observer. The best artificial light is afforded by the Welsbach burner or a thirty-two candle-power incandescent burner with a thoroughly frosted globe. While for convenience in general work the stand is tilted, when examining mounts of liquids, urine, hanging-drop culture, etc., the stand must be upright so that the stage is perfectly level. Place the slide on the stage and loosely secure it by the clips; so adjust the mirror as to illuminate the center of the field; without placing the eye to the eye-piece, rack the objective down until it almost touches the slide; then look into the instrument and perfect the illumination by adjusting the mirror again, if necessary; slowly focus *upward* by the coarse adjustment until a satisfactory focus is obtained; in moving the slide about, the fine adjustment will be all that will be necessary. *Never* focus downward until you have mastered the method just given; careless, or even at times the most careful, downward focusing will crush the slide or the lens by passing over the true focus and jabbing the objective into the slide. Before removing the slide, always rack the objective upward until it is at least ½ of an inch from the slide.

To use the $\frac{1}{12}$-inch oil-immersion objective: First, *with a lower power*, find and accurately center some object in the field upon which to focus; rack the tube upward until the objective is four or five centimeters from the slide; rotate the nose-piece so that the $\frac{1}{12}$-inch objective drops into the optic axis of the instrument. Place the stand erect so as to make the stage level. Place on the cover-glass a drop of cedar oil, at such a point that when the objective is racked down it will touch the drop of cedar oil at its center. The objective is now racked down into the cedar oil; looking into the instrument, adjust the light so that the field is well illuminated, the light uniformly

distributed, but not too brilliant or glaring; this, if present, should be overcome by closing the iris diaphragm until a soft, even illumination is obtained. Now, with the fine adjustment, slowly focus upward but one or two turns of the milled head; the object should come into view. If it is indistinct or hazy, try readjusting the iris diaphragm or the light, or the Abbe condenser may be moved downward or upward until the desired effect is secured. In examining stained specimens of bacteria the iris diaphragm is kept open; for unstained specimens it is choked down, admitting but little light. The successful study of any specimen is largely dependent upon securing perfect adjustment of all the parts of the microscope, and particularly the illumination. In case the field fails to clear up after careful adjustment of the instrument, examine the lenses to see that they are not dirty.

CHAPTER III.

BACTERIOLOGIC TECHNIC.

In order satisfactorily to study microorganisms we must be able to secure, and if possible to maintain, *pure cultures*, a term to be explained later. The soil upon which bacteria are grown is called a *culture medium.* The soils, or culture media, are classed under two heads—the **natural** and the **artificial**; of each of these we have two kinds, the *fluid* and the *solid.*

Natural Culture Media.—*Fluid:* Blood-serum, milk, urine, aqua coca, hydrocele fluid, eggs or egg-albumen, etc. *Solid:* Blood-serum, eggs, potatoes and other tubers, and fruits.

Blood-serum is the most valuable of all natural culture media, and may be used either in the fluid or in the solid state. The serum may be obtained from any of the lower animals, though that of the calf or ox is to be preferred. The blood is collected in clean jars at the time of slaughtering; a gallon fruit or museum jar answers the purpose. If the blood is passed directly from an artery into a sterilized jar, it will remain sterile. The freshly drawn blood is allowed to coagulate in the sterile receiver; it is then removed to the laboratory. A sterile glass rod is passed around the outside of the clot, between the clot and the jar, in order to detach the fibrin from the jar and to permit the clot to contract. The jar is then placed on ice. In from twelve to twenty-four hours the clot will have separated, and the serum may be siphoned off with a sterile siphon. If it is clear, it may at once be placed in tubes; if there be much suspended coloring-matter,—red blood-cells,—it may be set in the ice-box for sedimentation, after which the clear supernatant fluid may be poured into the culture containers. If this operation be conducted with proper care, the serum will not require sterilization, and may be used in its fluid state. In order to avoid infection the greatest care must be taken in every stage of preparation. Containers, pipets, instruments, hands, etc., must be sterilized with the greatest care and maintained in an aseptic condition. It is hardly necessary to say that such extreme care can rarely be taken, so that the Councilman-Mallory method (given below) has practically superseded this more tedious pro-

cess. If, however, a solid medium is wanted, the serum is sterilized and "set" by heating.

In order to sterilize blood-serum it must be heated one hour each day for four days; as high temperatures cause coagulation of the albumin, the heat had best not exceed 65° C. If it is desired to use it as a solid medium, the conversion from a liquid to a solid medium is accomplished by gradually raising the temperature until coagulation is just sufficient to render the serum solid; at this stage it is slightly opalescent, of a yellowish straw color, and easily penetrated by a needle. The temperature necessary for solidification rarely exceeds 70° C. Councilman and Mallory avoid the foregoing tedious process in the following manner:

Blood is collected in a clean jar; it is permitted to coagulate and the fibrin is detached, as already directed. The more or less clear serum is then siphoned off. The small amount of blood present does not interfere with the subsequent handling or with the use of the medium for culture purposes. Previously sterilized test-tubes, prepared as directed under Culture Containers (p. 80), are at once charged with the fresh serum. The tubes are placed in a slanting position in a dry-air sterilizer, the temperature of which is raised to 80° or 90° C. The heating must be gradual, and must not exceed the temperature given.

As soon as solidification is complete the serum is transferred to a steam sterilizer (the tubes being placed on end), and is sterilized at 100° C. for thirty minutes each day for three successive days.

Löffler's blood-serum mixture contains:

Bouillon containing one per cent. glucose, ... 1 part.
Blood-serum, ... 3 parts.

The two are mixed, placed in the tubes, and sterilized as directed for blood-serum. The medium is especially useful for the bacillus diphtheriæ, but may be used for almost any organism, and is, taken all in all, one of the best all-round media found in the laboratory. The advantages offered by the Councilman-Mallory method may be utilized in the preparation of this medium. The formula and preparation of bouillon are given with artificial culture media (p. 76).

Milk is a very useful culture medium. It may be alkaline, neutral, or acid; with the addition of an indicator it is used for testing the reaction of growing cultures. Test-tubes charged with the desired quantity of skimmed milk (all the fat should be removed) are thoroughly sterilized by exposure to steam. Cer-

tain bacteria may be identified by their peculiar action upon milk. Thus, some organisms induce coagulation of the casein, while others peptonize it; some develop an alkaline reaction, others an acid reaction.

While they are useful, the employment of urine, aqua coca, and hydrocele fluid is not general.

Boiled potato affords a splendid culture medium for the growth of many bacteria. Potato used as a culture medium is first thoroughly washed in water to remove dirt; it is then washed in a 1 : 1000 solution of corrosive sublimate, followed by sterilized water for ten or fifteen minutes to remove the mercury. The potato is then cut into slices. With an apple-corer pieces of the proper size are cut from the slices, slipped into sterilized test-tubes, and a small quantity of distilled water is added to prevent rapid drying after sterilization. Instead of using an apple-corer, the potato may be cut into a long, pyramidal piece resembling a gigantic exclamation point. The small end of the pyramid should be long, and should project downward into the water at the bottom of the tube, thus preventing desiccation of the upper part of the piece, upon which the culture will be made. The pieces are now ready to be sterilized, which may be accomplished by placing them in an autoclave for from twenty to twenty-five minutes; or, by fractional sterilization, for an hour a day, for from three to five days, in a steam sterilizer. They are now ready for inoculation.

FIG. 44.—MOIST CHAMBER FOR POTATO CULTURE.

To use this dish, or any similar chamber, for potato cultures, the dish is sterilized in a hot-air sterilizer and allowed to cool. In the bottom is placed a blotter, moistened with a 1 : 1000 solution of corrosive sublimate. The potato is cleaned as described in the text, and is sterilized whole; a thin knife, such as is shown on page 34, is also sterilized; the worker thoroughly disinfects his hands and takes the sterile potato in the left hand and the sterile knife in the right hand; the potato is then incised in its longest diameter, and, without separating the two halves, an assistant raises the upper half of the dish by the knob while the potato is quickly placed on the sterile blotter, the two halves being separated so that the freshly incised surface of each half is turned upward; the lid is now quickly replaced. If no growth occurs on the potato in three or four days, it may be considered sterile, and may be inoculated.

Sterilized eggs are occasionally used for the cultivation of anaerobic bacteria. The eggs are thoroughly sterilized at a low temperature, as already directed for blood-serum, a point in the shell is carefully penetrated with a sterile borer, the egg is inoculated, and the puncture is then sealed with wax. Occasionally, sterilization may not be necessary; but without it incubation can not well be applied, as the chick develops too rapidly. After inoculation the egg may be dipped in hot paraffin, which, on cooling, forms an air-tight covering.

Artificial Culture Media.—*Fluid:* Inorganic solutions, organic mixtures, bouillon, and vegetable and animal infusions. *Solid:* Bouillon, milk, etc., solidified by the addition of gelatin, agar-agar, or gelatin and agar-agar. To cultivate certain bacteria,—the tubercle bacillus, for instance,—it may be necessary to add glycerin to the medium.

The most useful artificial culture media are infusions of beef and mutton containing a small quantity of peptone. Most of the bacteria develop quite readily in such media. The stock culture medium is Koch's **alkaline-beef-peptone bouillon**. For ease

FIG. 45.—INSTRUMENT FOR CUTTING PLUGS OF POTATO FOR POTATO CULTURES.
The cut plugs are washed in water and pushed down into test-tubes into which the potato segment fits closely. Enough water is added to come just up to the lower end of the plug. The tubes are then sterilized as directed in the text.

and rapidity of preparation the following is recommended: Take an ordinary farina boiler (agate-ware is best), and fill the outside kettle with sufficient water to well inclose the inside can; into the latter put one liter of water, which had best be distilled; with a diamond or file mark on the side of the can the height of the fluid. Marks made on the side of the can are often difficult to find or to differentiate from other scratches, particularly when the can is more or less filled with steam and boiling fluids. An equally efficient and a somewhat simpler method is to take a glass rod and mark upon it the depth of the

fluid, subsequently maintaining the same depth by the addition of water. Obtain 0.5 of a kilogram of finely chopped lean beef from which the fat has been carefully removed; add this to the water, a little at a time, stirring constantly so as to make sure that every piece of the meat is well penetrated. The original directions required that this mixture macerate for twelve hours before proceeding with the next step. We do not now, commonly, find this necessary, although some workers apparently always macerate for the twelve or twenty-four hours, as originally advised. Whether we macerate or not, the next step is to add the peptone and salt. Take ten grams of Witte's dried beef-peptone and five grams of salt (sodium chlorid), and mix them thoroughly in a mortar or teacup; add just enough water to rub the mixed powders into a thin paste, which is now added to the meat-and-water mixture in the farina kettle and thoroughly stirred into the mass. The water in the outside kettle is now brought to a boil, during which time the mixture in the inside kettle has been frequently stirred. As soon as the albumin begins to coagulate the stirring is stopped, and when it is fairly advanced, after fifteen or twenty minutes' boiling the inside kettle is removed from its surrounding water-bath and its contents brought to a boil over the flame, care being taken that it does not boil over. The meat and coagulated albumin will collect into a rather dense mass, which should be broken up, so that the interior may be fully penetrated by the boiling fluid in order to extract the salts contained in the meat. After thirty minutes' boiling the mass is removed from the flame and strained through flannel. The water lost by evaporation must be made up by pouring enough cold water over the meat in the strainer to bring the filtrate to one liter. If any fat is seen over the surface of the fluid, as much as possible is removed with a spoon or by gently touching it with paper or a clean cloth. The filtrate will usually be clear, and, if not, it must be filtered. Tested with an indicator, this fluid will be found acid, and must be made neutral or faintly alkaline. This is best done by adding, drop by drop, a ten per cent. solution of

FIG. 46.—AGATE-WARE WATER-BATH (FARINA KETTLE).

Used in making culture media, and convenient for many purposes about the laboratory; the capacity should be about 1000 c.c. for inside boiler.

caustic soda (sodium hydroxid). The best indicator is a phenolphthalein solution, made by dissolving one gram of phenolphthalein in 1000 c.c. of fifty per cent. alcohol. A watch-glass containing about one centimeter of this solution is placed conveniently, and into this a drop of the bouillon is mixed, a different watch-glass being used for each drop; as soon as alkalinity is reached, the indicator turns a bright rose-color, which, while distinct, should be faint. Litmus paper may be used instead of the foregoing, but is less delicate, although for all ordinary purposes it is sufficiently accurate. With the disappearance of acidity the bouillon becomes faintly cloudy, the salts and albumins, insoluble in an alkaline fluid, precipitating. To complete the formation of this precipitate the fluid is thoroughly boiled for at least thirty minutes, and then filtered. It is advisable, when a perfectly clear fluid is absolutely essential, to cool the medium, filter, reboil, and again filter; this is rarely done, and is useless except that it assures the medium remaining clear; after each boiling, and before finally filling the culture vessels, the alkalinity of the fluid must be tested, for, in some inexplicable manner, a fluid previously known to have been neutral, or even alkaline, may become acid. When finished, the resulting fluid is known as neutral-, alkaline-, or acid-beef-peptone bouillon, the first word of the name always indicating the reaction. When intended for the cultivation of tubercle bacilli, glycerol (glycerin) is added (the amount commonly employed is six per cent.)—60 gm. of the glycerol, which must be weighed and not measured, to 1000 c.c. of the bouillon. It is now known as alkaline-glycerin-beef-peptone bouillon.

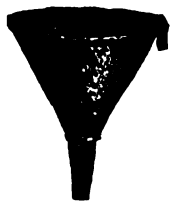


FIG. 47.—AGATE-WARE FUNNEL FOR FILTERING HOT FLUIDS.

Agate-ware has almost entirely superseded any other ware in the preparation of culture media.

Instead of the 0.5 of a kilogram of beef used in the above, two grams of meat extract (Liebig's or Armour's) may be substituted. The preparation is practically the same, except, of course, the flannel filter is not needed, and, as the meat salts are exceedingly difficult to remove, filtering while hot, and again when cold, may have to be frequently repeated to secure a perfectly clear fluid. Media prepared with an extract are not so satisfactory as those made from the beef direct. Streptococci grow indifferently or not at all upon media prepared from beef extract.

When it is desired to render the foregoing solid, gelatin or agar, or both combined, may be used.

Beef-peptone-gelatin.—To 1000 c.c. of cold bouillon add 100 gm. of gelatin ("gold-leaf," in sheets), torn or cut into fragments; macerate for fifteen or twenty minutes, until the gelatin swells up and becomes flaccid; it is then easily dissolved by gently heating in a water-bath; by the time it has reached a temperature that will not scald the fingers the gelatin will be dissolved. It is now removed from the water-bath and cooled until the fingers can be comfortably held in it for some time—about 50° C. or lower. When the gelatin is thoroughly dissolved, the fluid will require realkalinization; as gelatin is constantly acid, the previously alkaline bouillon is rendered acid. The alkalinization must be most carefully done, otherwise the gelatin may fail to solidify when finished. Again, one must be sure that all the gelatin is dissolved before alkalinization or, later, the reaction may be found acid. It must be but *faintly* alkaline. If by accident the fluid be made too alkaline, a few drops of dilute acetic acid will correct the error. When the reaction is found to be satisfactory, the white and finely broken shell of one egg is thoroughly mixed in with the gelatin; this is heated to the boiling-point in a water-bath, followed by boiling over the naked flame (which is best distributed by wire gauze) for at least half an hour; the water lost by evaporation is made up, and enough of the mixture filtered to half fill a good-sized test-tube; this is boiled repeatedly for several minutes, to see that all the albumin is coagulated, the reaction as desired, and that the gelatin remains clear; if so, the remainder is filtered and filled into test-tubes. When properly made, gelatin is the clearest solid medium at present attainable. It is liquid at temperatures above 22° C., and can not, for this reason, be incubated. As some bacteria liquefy gelatin and others do not, it constitutes a test culture medium of the greatest value.

Beef-peptone-agar.—Agar-agar is a gelatinoid substance derived from a Japanese seaweed. It is used for making culture media solid in the following manner: To 1000 c.c. of bouillon add ten grams of the agar threads cut into fragments not over two centimeters in length; place at once to boil over the naked flame, stirring frequently to prevent burning and the threads adhering to the bottom of the pan. It usually requires about an hour to secure perfect solution, without which filtration is impossible. Longer boiling does no harm, the quantity of the medium being maintained by adding, from time to time, enough water to compensate for that lost by evaporation. When fully dissolved, it is filtered. As it filters with much more difficulty than gelatin, and as the same precautions are necessary, I have deferred

the description until now. An efficient, heavy, preferably already folded filter (machine-folded filters are by far the best) is carefully opened and adjusted in the funnel; then, with the greatest care, thoroughly moistened with boiling water; a moment is allowed for the contraction of the filter, which always takes place; it is then again moistened with boiling water, the excess poured off, and the agar or gelatin poured down a glass rod on to the *side* of the filter—*not* into the center and never rapidly, as either will probably break the filter. In the case of agar it is best to have it boiling and add but 250 c.c. or less to the filter at one time, keeping the remainder hot in the water-bath and heating to boiling just before pouring into the filter. Gelatin can not be boiled very long or it may fail to gelatinize; with agar this danger is not present. Gelatin burns to the pan unless carefully watched; agar may do so, but less frequently. Gelatin should always be cleared by an egg; agar may be, but does not require it. Agar solidifies at about 42° C., and melts only at near the boiling-point; it is not so clear as gelatin, but, as it can be incubated, has many advantages. It remains solid when prepared with glycerin bouillon, which gelatin does not always do.

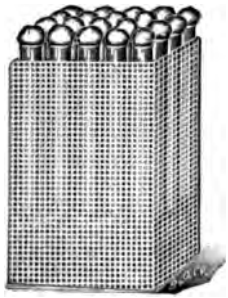


FIG. 48.—TEST-TUBE BASKET, MADE OF TINNED METAL, FOR HOLDING TEST-TUBES. These baskets should be 125 by 100 mm., and 150 mm. high.

Urine agar, which is particularly useful for the cultivation of the gonococcus, is made by using urine instead of bouillon. The urine is neutralized or rendered faintly alkaline, or it may be used in its acid condition. One per cent. of peptone and 0.5 per cent. of salt may be added, although this is not ordinarily necessary. After filtration, preliminary boiling, and filtration while hot and again when cold, the agar is added, dissolved, and filtered as already directed.

Culture Containers.—Cultures may be made in bottles, flasks, or test-tubes; the last two are the most used. If perfectly new, a thorough rinsing in clean water will suffice; if the tubes have contained cultures, or have in them cultures either growing or dead, they should be placed in the sterilizer for a couple of hours, with the cotton plugs in place; remove from sterilizer, take out the plugs, pour out the contents of the tubes, and boil one hour in a two per cent. solution of washing soda; wash with test-tube brush and rinse in several changes of clean water; rinse in a one per cent. solution of hydrochloric acid; carry

through several changes of water, and set up to dry with bottom upward. When dry, plug with cotton; for this purpose we use ordinary cotton batting, clean and free from the cotton hulls. Absorbent cotton possesses no advantages. A more or less square or octagonal disc of cotton, about ten centimeters in diameter, has its corners folded into the center so as to make a plug twice as long as the diameter of the tube or the neck of the flask. The plug should fit so tightly that the tube or flask can be lifted safely by the cotton plug, which should enter the mouth to a distance equal to twice the diameter of the tube or the neck of the bottle or flask, and should project at least one centimeter.

FIG. 49.—DOUBLE-WALL HOT-AIR STERILIZER, FOR STERILIZING TEST-TUBES, GLASSWARE, AND OTHER LABORATORY APPLIANCES AND INSTRUMENTS.

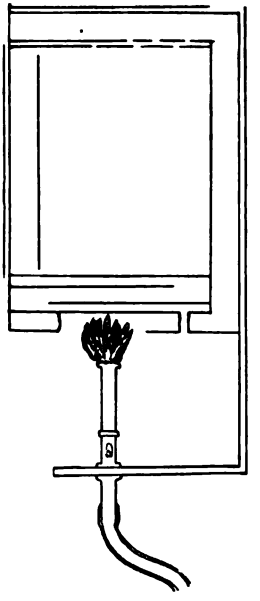


FIG. 50.—DIAGRAM OF INTERIOR OF HOT-AIR STERILIZER.—(*Coplin and Bevan.*)

The construction must be such that a jacket of hot air surrounds the inside chamber, and thereby assures an equal distribution of heat to the interior.

The test-tubes used for cultures should be of the best Bohemian glass, with a lumen of 13 mm. to 15 mm., and 130 mm. to 150 mm. in length. The flasks should be of the Erlenmeyer form, with a capacity of 100 c.c. Larger sizes, 250 c.c. to 1000 c.c., will be needed for storing media.

After clearing and plugging, the tubes and flasks are put in the hot-air sterilizer for twenty minutes at 130° C. In the ab-

sence of a hot-air sterilizer any cooking oven may be used, leaving the tubes in the oven until the cotton just begins to brown, a temperature which approximates 140° C. The tubes are now ready to receive the medium. An ordinary percolator or funnel has a rubber tube ten centimeters long, connected to the tubulature at the bottom by means of a perforated cork and a short glass tube; at the lower end of the rubber tube a second glass tube is connected so that it projects about ten centimeters below the rubber tube; the latter is then collapsed by means of a thumb pinch-cock (Mohr's spring pinch-cock) applied to the rubber tubing between the ends of the two glass tubes. The liquefied medium is poured into the percolator; the test-tubes are then arranged in the baskets at the side of the percolator. A test-tube or flask is grasped by the left hand, preferably by the thumb and index-finger; the cotton is rotated and loosened by means of the thumb and index-finger of the right hand, and removed by grasping the projecting tip between the ring- and little fingers of the right hand; the tube is now carefully slipped over the filling tube from the percolator, *care being taken that no fluid comes in contact with that portion of the tube into which the cotton plug is to go;* relax the pinch-cock and admit to the test-tube or flask the desired quantity; close the pinch-cock, remove the tube, *using the same care to avoid wetting the mouth of the tube*, and reinsert the cotton plug. This is repeated until the desired number of tubes or flasks are filled. If any of the medium remains, it may be run into a flask, sterilized as will be directed later, and, preserved for future use. The amount of medium placed in each tube varies with the medium and the purpose for which it is intended. For some experiments a measured quantity will be needed, but for ordinary purposes the tube should be about half filled with bouillon or gelatin, and with agar to a depth equal to a little more than twice the diameter of the tube. Flasks

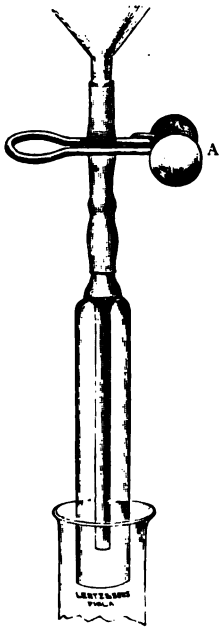


FIG. 51.

Apparatus to be attached to the lower end of a funnel, as shown in the cut, for use in filling test-tubes. The outside glass tube prevents the medium that flows from the inside tube from coming in contact with the mouth of the test-tube during introduction or withdrawal. A. Mohr's spring pinch-cock.

should never be more than half full when intended for culture, and often very much less will be sufficient.

Sterilization.—The Arnold steam sterilizer or the autoclave is used. If the former is used, fractional sterilization is best, keeping filled tubes in the steam chamber, at 100° C., thirty minutes a day for three successive days; in the intervals between sterilizations they are kept at room-temperature. The object of this is to destroy all organisms in the adult or fully developed stage. It is known that spores are not destroyed by a temperature of 100° C. unless it be very long applied; any spores that escape the heat on the first day have time to develop by the second day, or, to assure their being caught, a third sterilization is resorted to. Experience teaches that this is usually sufficient; however, the tubes should be watched for three or four days, and if any of them show a growth, the process should be repeated for all.

FIG. 52.—ARNOLD'S STEAM STERILIZER FOR STERILIZING CULTURE MEDIA, ETC.

By means of the autoclave a temperature of 130° C. is obtained in the steam chamber, which, in from twenty to thirty minutes, destroys both fully developed bacteria and their spores; it is of great convenience for bouillon, agar, potatoes, milk, and many other culture media, but can not be used for blood-serum or gelatin. The latter usually fails to gelatinize after being subjected to the high temperature; indeed, gelatin must always be sterilized with the greatest care, as prolonged exposure, even to the temperature of 100° C., should be avoided. Potatoes require prolonged exposure to high temperature, as they usually contain earth organisms difficult to destroy.

In order to increase the surface area of media containing agar or blood-serum, the tubes, while the medium is in a liquid state, are inclined with the mouth just high enough to prevent the agar flowing up to the cotton; when "set," they may be stood on end, as other tubes.

To Prevent Stored Media from Drying.—For this purpose the writer has tried rubber caps, rubber tissue, oiled paper, cork and rubber stoppers, and the paraffin method, none of which seems fully satisfactory. One of the best methods is to trim the cotton even with the top of the tube, and push it down 0.5 cm. below the tube-lip; take a coin of proper size to just drop inside of the lip of the tube; heat the lip of the tube and the body of the tube as far down as the cotton extends, until the cotton is slightly browned, and at the same time heat the coin; drop the coin upon the tube, and, while still warm, seal it to the tube at

FIG. 53.—ARNOLD'S STEAM STERILIZER, BOSTON BOARD OF HEALTH FORM.
This is the most convenient and the best sterilizer for general laboratory purposes.

the margin, using for this purpose a good quality of stationer's sealing-wax. This process is tedious, and is most useful for tubes containing cultures that require long incubation, such as the tubercle bacillus. A much more useful plan, and one almost as efficient, consists in pushing the cotton down, heating the mouth of the tube and inclosed cotton, and placing over the end a disc of quite thick tin-foil, which is evenly folded over the lip of the test-tube. For this purpose commercial tin-foil, which contains a relatively large proportion of lead, may be used, as it is much cheaper than chemically pure tin. Such a cap is easily

removed and replaced. It offers all the advantages of rubber, and can, if sufficiently heavy, be readily sterilized.

Dunham's Peptone Solution.—Rub up in a mortar five grams of salt and ten grams of peptone, with enough water to make a paste; finally, dilute to 1000 c.c., boil, and filter. As a rule, the filtrate is neutral or alkaline; in either case, after sterilizing as already described for bouillon, it is ready for use.

For plating it is always best to have on hand a number of tubes of gelatin and agar, each tube two-thirds full.

FIG. 54.—AUTOCLAVE, OR DIGESTOR, USED FOR STERILIZING BY STEAM UNDER PRESSURE. The lid is held in place by three winged nuts, which are thrown down to the side in order to raise the lid. The solid copper chamber on the inside has placed in it two liters of water, and the material to be sterilized is placed upon the tray with perforated bottom shown at the side of the cut; this is then placed inside of the autoclave, and the lid is closed down and secured by the winged nuts; the gas is now lighted and the heat applied until steam escapes from the small cock at the left, which is then closed. The pressure within the apparatus now rises until the safety-valve, which may be set at any pressure, blows off. Sterilization by this means may be secured, at temperatures ranging from 100° C. to 140° C., in from twenty to forty minutes.

Pure Cultures.—A pure culture is one containing the progeny of a single germ; for example, a pure culture of the tubercle bacillus must contain no other germ. When two kinds of bacteria are growing together, the culture is said to be a *mixed culture*. Under nearly all conditions various organisms are found together, and in order to separate them we must resort to **plating.** The object to be attained is the separation of each germ, in order to enable it to grow into a colony by itself; so

that, if the original mixture contained three kinds of bacteria, we may obtain three kinds of colonies, and from these obtain cultures which have but the one variety—that is, a pure culture of each.

Bottle Plates.—Any strong, clear, flat-sided bottle will do. The capacity should be about 500 c.c.; clean, plug with cotton, and sterilize in hot-air sterilizer; charge with gelatin or agar, usually about twenty cubic centimeters. Sterilize as already directed for culture media, and set the bottle aside until wanted for plating; to prevent drying of the medium, the cotton may be pushed downward in the neck so as to admit a short rubber stopper, or the neck and lip may be covered with tin-foil as already directed. As a rule, the bottle will be used within one month, during which time it should not become dry. When ready for use, at least three bottles will be needed. Liquefy the medium in the sterilizer or water-bath; cool to 50° C. or below, inoculate the first bottle with a small loopful of the mixed culture or suspected material, as pus or blood, stopper the bottle with the cotton plug, and shake, to thoroughly mix; inoculate the second bottle by carrying a loopful from the first to the second, replace the plug, and shake; and in the same manner inoculate a third bottle from the second, and shake as before. Lay the three bottles on the flat side; the medium will spread out and cover the side of the bottle; label the three bottles *a*, *b*, and *c*, the first being *a*.

FIG. 55.—BLAKE BOTTLE, USED FOR BOTTLE PLATES.—(*Coplin and Bevan.*)

Petri Dish Plates.—Three or more test-tubes containing sterile agar-agar or gelatin, filled to within an inch or so of the cotton, as already directed, are placed in a water-bath or a sterilizer and the contained medium liquefied; while this is in progress an equal number of Petri dishes are sterilized in the hot-air chamber and allowed to cool. The liquefied medium is cooled to under 50° C. A tube is inoculated with the material to be plated, as directed for bottles; from the first tube a second is inoculated, and from the second a third, and so on, each tube having the medium thoroughly mixed by using the inoculating needle as a stirrer. Remove the cotton from the first tube and pass the lip of the tube through the

FIG. 56.—DISH DEVISED BY PETRI. Used almost exclusively for plating; the most convenient diameter is from 100 to 120 mm.

flame; raise the lid of a sterile Petri dish just enough to get the mouth of the tube under it, and quickly pour the contents of the tube into the dish, which is then gently tilted from side to side, allowing the medium to flow over the bottom and cover it fully. A second dish receives in the same way the contents of the second tube, and so on, through as many tubes as may be desired. The plates are labeled as directed for the bottles.

Esmarch's Tube Plates.—Three or more tubes of sterile agar or gelatin, each tube not containing more than two or three cubic centimeters of the medium, are liquefied and inoculated as directed for the Petri dish method. A block of ice, with a flat or nearly flat upper surface, has a channel made in it by laying a test-tube of the same size as those to be used, filled with hot water and corked, upon the top of the ice, the corked end projecting beyond the edge of the ice; this tube is rolled over and

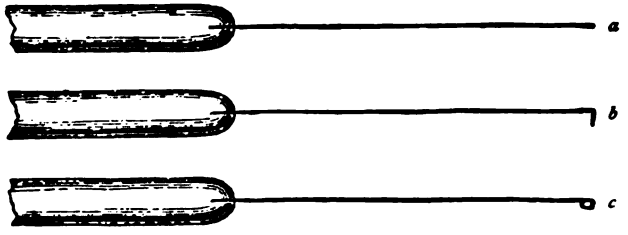


FIG. 57.—PLATINUM INOCULATING NEEDLES MOUNTED IN GLASS RODS.
Showing the shape of the ends as may be found useful for: *a*, stab cultures and stroke cultures; *b* and *c*, stroke cultures and smear cultures.

over in the same spot until a channel is so made as to half bury the tube, the bottom end being a little lower than the corked end. Into this channel one of the infected tubes is laid so that the medium flows up to within two centimeters of the cotton but *does not touch it;* the tube is then rolled, at first slowly, then more quickly, until, within the first minute, it is spun rapidly; the medium is in this way congealed over the entire inside of the tube nearly up to the cotton; if the latter comes in contact with the medium, it prevents easy removal of the plug by making it stick to the side of the tube. Each tube is treated in the same way, after which it is labeled as directed for other plates. When set, the tubes are placed on end. With gelatin this can be quickly done; with agar, however, the tube must be kept in a nearly horizontal position for several hours, generally overnight, otherwise the agar may slip down.

After the plates are made by either of the foregoing methods

we have to await the growth of the colonies ; agar may be incubated. At the end of a varying period the colonies appear as

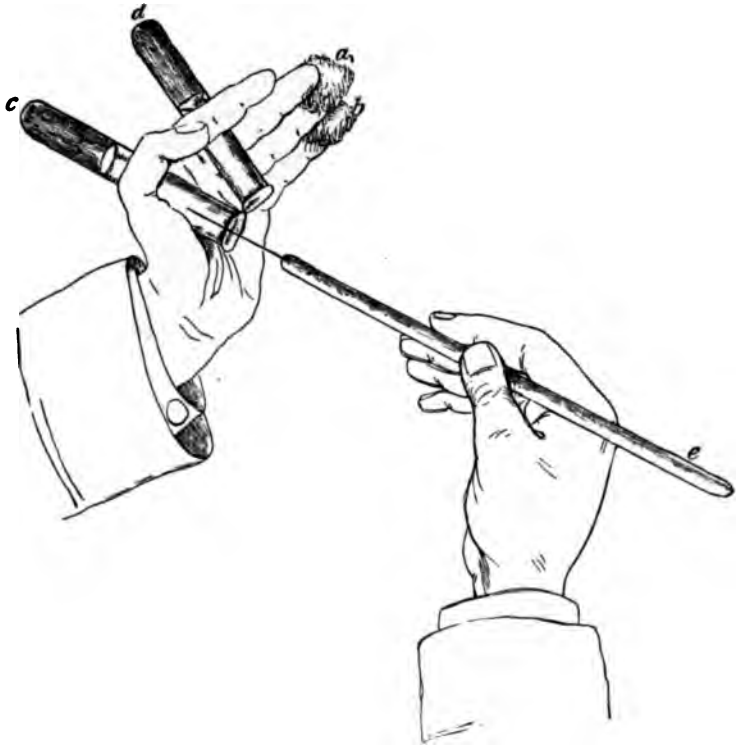


FIG. 58.—METHOD OF HOLDING TUBES, COTTON, AND PLATINUM WIRE WHILE INOCULATING SOLID MEDIA.—(*Koch's method, modified from Woodhead.*)

The tubes *c* and *d* are grasped as shown in the illustration. The cotton from *d* is removed with the thumb and index-finger of the right hand, and held between the ring-finger and little finger of the left hand, at *b* ; that portion of the cotton which was within the tube is not touched by the fingers, but is directed upward. In the same way the cotton is now removed from the tube *c* and grasped by the ring-finger and middle finger, as at *a*, the same precautions being used as described for the other tube. The lips of the tube are now passed quickly through the flame of a Bunsen burner, to remove any adhering dust, and the platinum wire and the glass rod are sterilized in the flame, the rod being heated to a greater distance than it is expected to enter the tube. Supposing that *d* is the tube from which it is desired to remove the culture, and *c* is to receive it: the platinum wire, while still warm, is thrust into the culture medium to one side of the growth to cool the needle: the growth is then touched by the needle, thus infecting the needle, which is quickly withdrawn and the tube *c* inoculated; ***immediately upon the withdrawal of the inoculating needle*** the cotton stoppers are placed in their respective tubes, and the ***needle is at once sterilized*** and set aside. ***Never lay down an infected needle!*** The tube inoculated is labeled, dated, etc., and set aside for observation. All this can be done quickly, and the beginner should practise the manipulation on tubes of media which are not infected ; if they become infected during the process, his technic is faulty, and should be perfected before working with pure cultures.

distinct dots in and on the culture medium. In plate *a* they will commonly be too close together to be distinct ; plates *b* and *c*

will be better. Selecting a colony which is alone, transplant this into a test-tube in the following manner:

Take the platinum needle and heat its entire length to redness, at the same time heating all of the attached glass rod that is likely to go into the test-tube, bottle, or dish. If the colony to be removed is within a bottle or test-tube, it will be best to bend

FIG. 59.—METHOD OF HOLDING TUBES, COTTON, AND PLATINUM WIRE WHILE INOCULATING LIQUID MEDIA.

The steps and the lettering are the same as in previous figure. The right hand should not be over the tubes, as it appears in this illustration, but the tubes in the left hand should be so inclined that there will be but little danger of anything dropping into them.

the tip of the inoculating wire like the letter L; immediately after sterilizing the needle, holding it like a pen in the right hand, take the bottle and test-tube or both test-tubes in the left hand; remove the plugs from the tubes or bottles by grasping the projecting cotton of both tubes between the middle finger and ring-finger and the ring-finger and little finger of the right hand; pass the lip of the bottle or tube through the flame to burn off

any adhering dust; pass the needle into the bottle or tube, and lightly touch the colony from which it is desired to obtain a culture; this will infect the needle; quickly withdraw the needle and pass it into the tube upon which it is desired to inoculate the growth. The inoculation made may be: (*a*) a **streak** or **stroke culture,** in which case the needle is drawn from below upward in a straight line over the slanting surface of an agar or blood-serum tube; (*b*) a **smear culture,** made by gently rubbing the infected wire over the surface of the medium; or (*c*) a **stab culture,** made by a straight needle-thrust, from above downward, through the medium. Stroke and smear cultures are the most used on all solid media except gelatin, in which stab cultures are best. In transplanting from a Petri dish culture, the lid is raised barely enough to introduce the previously sterilized needle, which is then touched upon the colony, removed, and applied to the culture tube as previously directed.

The platinum needle used in bacteriologic work consists of a platinum wire, from one millimeter to two millimeters in thickness and from five centimeters to eight centimeters in length, fused into the end of a glass rod about five millimeters in thickness and from fourteen centimeters to eighteen centimeters long. The rod is used as a holder or handle for the loop. The latter is variously curved, looped, or may be used straight, as for stab cultures. (See Fig. 57.)

Bacteriologic Examination of Water and Other Fluids.* —Sterilize a container in the hot-air sterilizer, and collect the water for examination. As bacteria multiply very rapidly, the examination should be made as soon as possible after collection; after a few hours' standing, particularly if the weather be warm, the results obtained will be without value as to quantity of bacteria.

Prepare a dozen Petri dishes and a corresponding number of tubes for plating. Sterilize two burets so graduated as to accurately measure 0.02 to 1 c.c.

Thoroughly agitate the water in order to diffuse the bacteria equally throughout the specimen, and fill a sterile buret with the sample under examination. The test-tubes of media, gelatin, or agar having been fully liquefied, are cooled to 45° C. in a water-bath; to each of two of the tubes is added 0.02 c.c. of

* Bacteriologic examinations of water and air are introduced here as being good examples of the practical application of improved plating methods, and in order that the student may familiarize himself with the technic of preparing plates and securing pure growths therefrom.

the infected water; to another pair of tubes 0.05 c.c. of water is added; to another, 0.075 c.c.; to another, 0.1 c.c.; to another, 0.5 c.c.; and to another, 1.0 c.c. The tubes are thoroughly shaken, immediately poured in the usual way, and set aside for the colonies to develop. If agar has been used, the plates

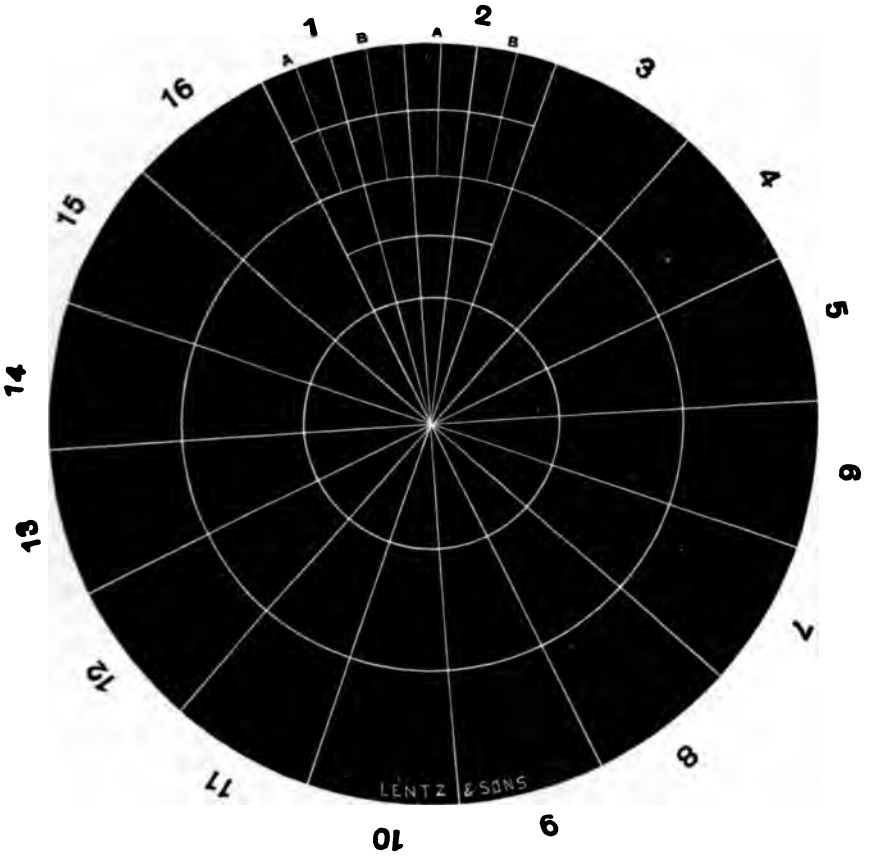


FIG. 60.—APPARATUS FOR COUNTING COLONIES.
Petri dishes are placed upon the ruled circle, and the colonies counted as directed in the text. An ordinary slate may be ruled as in the above figure and used for the same purpose.

may be incubated. As soon as the colonies develop they are counted. A Petri dish counting apparatus may be used, or a slate upon which has been ruled a diagram like that shown in figure 60. All the colonies in the plate may be counted or the number determined in one, two, or more of the wedge-shaped areas

bounded by the radii and the arc, and the resulting number found for one wedge-shaped area multiplied by the total number of divisions—sixteen. The number of colonies found in the whole plate represents the number of bacteria in the water used for the plate. For example: Several areas counted give an average of twenty colonies to each area; there are sixteen areas: 20 × 16 = 320, the total number of colonies in the plate; assuming that the quantity of water used in making the plate was 0.1 c.c., then one cubic centimeter will contain ten times 320 or 3200 bacteria. If different quantities of water are used, the result, reduced to the unit,—say, one cubic centimeter,—should be approximately the same, one series being a control for another.

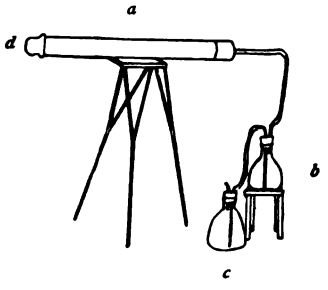


FIG. 61.—HESSE'S AEROSCOPE.

This consists of a hollow cylinder of glass, *a*, sixty centimeters in length, four centimeters in diameter, plugged with cotton at both ends, sterilized, and charged with a layer of culture, much as the Esmarch plates. The two ends are covered by caoutchouc, one of the rubber caps having a hole to admit a glass tube by which the tube *a* is connected with the gravity flask *b*, which is further connected to the flask *c*. The flask *b* is filled with water. When ready for use, the rubber cap and the cotton plug at *d* are removed, the flask *b* is tilted so that the contained water flows into the flask *c*, thereby aspirating as much air into the tube *a* as water is allowed to flow from the upper to the lower flask. The tube *a* is now plugged and set aside for colonies to develop. These can be counted and transplanted as in other plate methods. Petri has improved the foregoing by substituting for the tube *a* a short tube packed with sand and sterilized, aspirating air through it, and then mixing the sand with gelatin and pouring into plates. Sedgwick and Tucker use sterilized granulated sugar instead of the sand. The sugar and sand methods give the best results.

In the examination of sewage and of other materials exceedingly rich in bacteria the large number of organisms present in even the smallest, most easily measured quantity may be too great for the satisfactory counting of the colonies after their development on plates. To avoid this difficulty, the material to be examined is diluted with an equal quantity of sterile water; should this not be sufficient, further dilutions may be made. In the final calculation the dilution must be taken into consideration.

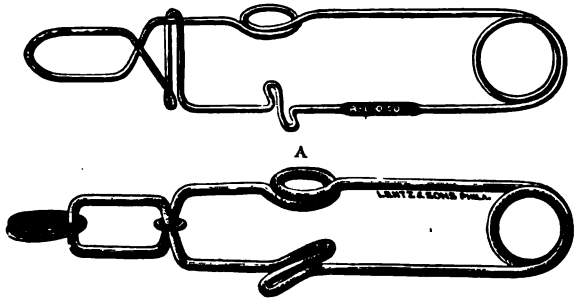
The foregoing test determines the number of bacteria in the sample. If it is desired to find what germs are present in the water, to make the test complete, the colonies are transplanted and studied as already directed when considering pure cultures. (See table illustrating the method of recording principal characteristics of an organism, p. 116.)

Bacteriologic Examination of Air.—The principle upon which

the examination is conducted is to depend either upon sedimentation upon a sterile surface, as a Petri dish containing media,—a very unsatisfactory method,—or to secure the bacteria in a sterile filter by aspirating through it a known volume of air. Figure 61, with the attached legend, will explain the methods used.

Staining Bacteria.—Staining bacteria greatly facilitates the study of their morphologic characteristics. For this purpose the anilin dyes are almost exclusively used.

The anilin stains commonly used in the laboratory are fuchsin, gentian-violet, methyl-blue, and a few others; they are all applied in practically the same manner. For stock, it is best to keep the dye as a saturated alcoholic solution. For staining, however, alcoholic solutions are of little value, as they do not seem to



FIGS. 62 AND 63.—TWO FORMS OF STEWART'S COVER-GLASS FORCEPS.

Method of holding cover-glass and applying the stain. Convenient for blood work, and absolutely necessary for bacteriologic work; useful also in sputum examination, etc. The lower instrument shows a cover-glass with stain in position. If the cover-glass be grasped with the film or spread side toward the side of the forceps that has the circular bend intended to fit the thumb, shown at A, there will be no danger of losing trace of the side containing the spread, as this side of the forceps is practically always upward.

possess the penetration of watery solutions. The usual strength of solution is two per cent. of the dye dissolved in water; as the dyes are disagreeable to handle, the solutions are commonly prepared by taking a test-tube, from thirteen to fifteen millimeters in diameter, filling it about two-thirds full of distilled water, and adding the saturated alcoholic solution of the dye, drop by drop, until the water is so colored that, by ordinary diffuse light, one can barely see through it. This is then poured into a bottle adapted with a Barnes dropper. (See cut of appropriate stain bottle, p. 65.) The solution so prepared is about 1.7 per cent., and may be used whenever a one or two per cent. solution of the dye is recommended. The addition of carbolic acid to aqueous solutions of some anilin dyes seems to increase

their staining power and keeping properties. For this reason, instead of using plain distilled water, as previously recommended, many workers use a five per cent. aqueous solution of chemically pure carbolic acid. It is of the greatest importance that the carbolic acid should be chemically pure, as many of the samples of commercial carbolic acid contain contaminants and extraneous chemic bodies that are injurious to the anilin dyes.

One of the most useful stains is the *Koch-Ehrlich anilin-water solution.* This should be freshly prepared each time it is wanted, as it will not keep. Take, in a test-tube, about twenty cubic centimeters of distilled water; add anilin oil, drop by drop, shaking thoroughly until no more of the anilin is dissolved, the drops floating on and in the water, which may become milk-like as the result of emulsification of the oil; filter until clear: usually one filtration will be enough, but occasionally two or three will be required.

Formula for stain:

Saturated solution of anilin oil in distilled water, . .	100 parts.
Saturated alcoholic solution of gentian-violet, methyl-violet, or fuchsin, ...	11 "
Alcohol, ...	10 "

As it is not desired to stain laboratory utensils any more than can be avoided, it has been found that practically the same results as those secured by measuring can be obtained by dropping the solutions: 100 drops of the anilin water, 21 drops of the alcoholic solution of the dye, and 20 drops of alcohol.

Löffler's Alkaline Methyl-blue Solution:

Saturated alcoholic solution of methyl-blue, ...	3 parts.
Aqueous solution of caustic potash (1 : 10,000), . .	100 "

Ziehl's Carbolfuchsin.—For formula, see page 67. This is probably the most useful bacterial stain yet introduced.

To Stain Bacteria.—Thoroughly cleanse a cover, dry, and polish it; grasp it with a cover-glass forceps and pass it through the flame a number of times to burn off any bacteria or other organic material that may be on it; avoid heating too much, as the cover may warp or crack. Spread on this, with a previously well-sterilized platinum loop or needle, a thin film of the material; permit it to dry *without using any artificial heat.* It is then "fixed" by passing through the flame, as follows: Stand about thirty centimeters from the flame and carry the cover-glass through a circle, the diameter of which is represented by the distance between the flame and the worker; pass it through the flame three times. Stain from two to ten minutes; wash thoroughly

in water, dry, and mount with the film side downward. Films must be thoroughly dried before mounting; evaporation of the water accomplishes the same result as the application of alcohol in sections—dehydration; the use of a clearing agent, such as creasote or cedar oil, is usually unnecessary, as the residual oil present in the balsam will clear satisfactorily, provided the film is dry. The presence of either alcohol or water in the film when mounted on balsam leads to more or less clouding, owing to the emulsification of the residual oil in the balsam.

Temporary mounts are often made, thereby avoiding the use of reagents so disagreeable and sticky as damar or balsam. If the examination is to be made with a dry mount, the film is turned over, with the spread side downward, into a drop of water, the excess of which is removed to prevent the cover-glass from floating. When an oil-immersion lens is to be applied, the

FIG. 64.—KALTEYER'S COVER-GLASS FORCEPS.
This instrument may be used exactly as the forceps shown in figures 62 and 63; in addition, it may be used as in the illustration. The danger of forgetting which side of the cover is coated is less than with any other type of forceps.

most satisfactory temporary mounts are made in the same oil as used for immersing the objective. The thoroughly dried film receives in its center a droplet of the oil, and is then inverted on the slide; a droplet of oil is placed on its upper surface, and the examination is proceeded with in the usual manner. For method of focusing immersion objective, see page 71. Spreads may be made directly on the slide, followed by fixation, staining, etc. Such spreads may be examined without a cover-glass—a method commonly in vogue, but one with which the writer is not in sympathy.

Weigert's Method for Sections of Tissue Containing Bacteria. —Place sections for from six to eighteen hours in a one per cent. aqueous solution of any of the basic anilin dyes; after removal from the stain, wash in one-half saturated solution of potassium carbonate, then in distilled water, next in **sixty per**

cent. alcohol, and finally dehydrate in absolute alcohol. Clear in oil of cloves, xylol, or cedar oil, and mount in xylol balsam. Heating the stain or using a stronger solution will hasten the staining process, though it may not be so satisfactory. In case the particular basic dye used gives an unsatisfactory result another should be tried, using the same formula and method.

Gram's method may be used either for cover-glass films, prepared in the usual way, or for sections. Stain in the Koch-Ehrlich solution, made with gentian-violet (see p. 94), from two to five minutes, in most cases; to twelve or twenty-four hours in others; rinse for a moment in water, and apply Gram's solution.

Gram's Iodin-iodo-potassic Solution:

Iodin,	1 part.
Potassium iodid,	2 parts.
Distilled water,	300 "

In films, after one or two minutes, the iodin solution is washed off with water, followed by alcohol. From time to time the cover may be mounted in water and examined with a $\frac{1}{6}$-inch or $\frac{1}{8}$-inch objective, and as soon as the excess of dye and precipitate has been fully removed, it may be dried and mounted in xylol balsam.

As soon as the section becomes a dark brown, wash in sixty per cent. alcohol, dehydrate in absolute alcohol, continuing the latter as long as any perceptible amount of color is discharged, clear in oil of cloves or cedar oil in which a small amount of color may be discharged, pass through one or two changes of xylol, and mount in xylol balsam. After washing in sixty per cent. alcohol, sections may be contrast stained with carmin or hematoxylin, or with a one per cent. aqueous solution of vesuvin or Bismarck brown.

Veisser's method of spore staining consists in preparing the cover-glass as before, floating it upon the Koch-Ehrlich solution (made with gentian-violet) in a watch-glass, and heating to near the boiling-point for an hour. The film is next washed in water and decolorized by a solution composed of twenty-five parts of hydrochloric acid and seventy-five parts alcohol. This removes the stain from the bacilli, but if not allowed to act too long, leaves the spores stained. The preparation is next stained with methylene-blue, washed in water, dried, and mounted.

Flagella Staining.—Löffler's method requires two fluids, the first being a mordant, the second the stain. First solution consists of:

Aqueous solution of tannin (20 gm. tannin to 80 c.c. water),	10 c.c.
Aqueous solution of ferrous sulphate, saturated in the cold,	5 c.c.
Saturated alcoholic solution of fuchsin,	1 c.c.

The coloring solution is composed of saturated solution of fuchsin in anilin water, to which are added a few drops of caustic soda (1 : 1000) until opalescence commences. The mordant is applied to the cover-glass film, heating slowly over the flame for one minute. It is not necessary for the liquid to boil. Wash in distilled water and then in alcohol. Stain by placing on the film a drop of the alkaline staining solution, heating again gently for one minute; wash in distilled water, dry in air, and mount.

Different species of bacteria require an acid or alkaline reaction to the mordant, and for this purpose two solutions are necessary: (1) Caustic soda, one per cent. aqueous; (2) an aqueous dilution of sulphuric acid, of which one cubic centimeter will just neutralize one cubic centimeter of the alkaline solution. For spirillum of cholera, one-half to one drop of the acid solution to sixteen cubic centimeters of the mordant; for bacillus typhosus, two cubic centimeters of the alkali to sixteen cubic centimeters of the mordant, and so on; the number of drops of either solution can be determined only by experiment upon the organism in question. The bacillus pyocyaneus and many varieties of the spirillum require an acid reaction, while the bacillus typhosus, bacillus subtilis, bacillus of malignant edema, and bacillus of symptomatic anthrax require an alkaline reaction.

Pitfield has recommended the following stain for flagella, using but one solution for mordant and stain:

(A)	Saturated aqueous solution of alum,	10 c.c.
	Saturated alcoholic solution of gentian-violet,	1 c.c.
(B)	Tannic acid,	1 gm.
	Distilled water,	10 c.c.

These are made separately, filtered, and mixed. The resulting mixture—stain and mordant combined—is applied and heated gently almost to boiling-point, washed in water, dried, and mounted.

McCroric's flagella stain is a one-fluid stain having the following composition:

Night blue, saturated alcoholic solution,	10 c.c.
Tannic acid, 10 per cent. aqueous solution,	10 c.c.
Alum, 10 per cent. aqueous solution,	10 c.c.

Spreads are made from cultures eighteen to twenty-four hours old; the film is dried and fixed as usual. The stain is applied for two minutes cold and then warmed until a faint haze of steam is given off. Wash thoroughly in water, dry, and mount in balsam. Of the many stains for flagella that have been advised, this seems to yield the best results.

Microscopic Examination of Stained and Unstained Mounts.—In tissues stained by any of the methods given, the location, under a low power,—$\frac{1}{6}$-inch objective,—of bacteria can often be inferred by agminated areas of the stain known to stain such organisms. Having located such an area, a higher power may be used. Always begin the examination with a low power.

(For description of microscope and method of using same, see pp. 69 to 71.)

Gas Formation.—The development of gas may well be investigated in connection with our study of yeasts. Thus, if a saccharometer charged with a sterile culture fluid containing glucose be inoculated with the saccharomyces cerevisiæ, gas will collect in the measuring-tube, showing its production by the growth of the yeast. In addition to the production of gas, it can be shown that the fluid contains other substances; simultaneously with the gas production alcohol is elaborated. The equation is written as follows:

Glucose	=	Alcohol	+	Carbon Dioxid.
$C_6H_{12}O_6$	=	$2C_2H_6O$	+	$2CO_2$

The study of gas formation is conducted for other organisms after the same method as described for the yeasts; while saccharine fluids are mostly used for this study, other media have also been found available.

Gelatin or agar *shake cultures* are sometimes used to detect gas formation. Either medium is liquefied, cooled to below 50° C., and inoculated while liquid; it is then thoroughly agitated and allowed to solidify. The growth of organisms producing gas will be evident by the appearance of small bubbles throughout the medium. The test is, at times, facilitated by using a medium containing glucose, in which case the reaction may be identical with that previously described; in many cases it is, however, a much more complex problem.

Anaerobic Cultures.—*Novy's Apparatus* (Fig. 65).—Petri plates, Esmarch plates, or culture tubes are placed inside, the dome, *B*, is put in position and secured by the vise-like clamps, *D*, *D*; the glass stopper is turned, as shown in the cut. The tubulature not having the L-shaped extension down-

ward is connected with the hydrogen generator, and a constant stream of gas is carried through the apparatus for some hours. As soon as the air is displaced, the stopper, *C*, is turned one-fourth of a turn, thus cutting off the connection between the tubulatures on the side of the neck and the inside of the apparatus. If carbon dioxid is used instead of hydrogen, it is admitted through the tubulature that communicates with the in-

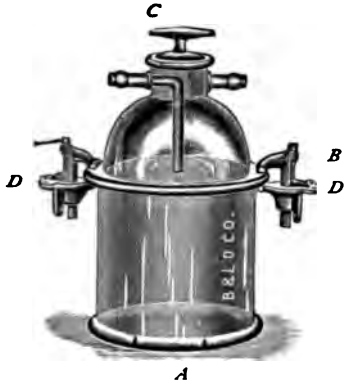


FIG. 65.—NOVY'S APPARATUS FOR ANAEROBIC CULTIVATION OF PLATES AND TEST-TUBES.

The apparatus consists of the following parts: *A*, the base, a solid glass cylinder having a capacity of about one liter and ground at its upper edge with a flange to make an air-tight joint with *B*, the dome, the two being clamped together by the vise-like clamps, *D*, *D*, the joint being more perfectly assured by rubber bands. The top of the dome, *B*, arches into a neck like that of a bottle, and is closed by *C*, which is an ordinary ground-glass stopper ground into the mouth of the neck, to the dome *B*. Through the side of the glass stopper, C, are two openings, so arranged that when *C* is turned as shown in the cut the openings permit gas to pass into the interior of the apparatus through either of the tubulatures shown at the side of the neck. On the inside of the stopper an L-shaped tube is fused, so that any gas carried into the apparatus through that tubulature passes below the level of the opposite tubulature.

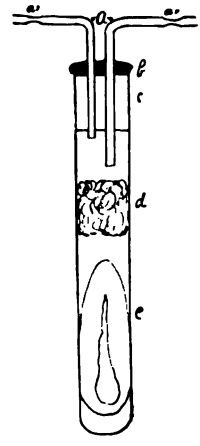


FIG. 66.—STERNBERG'S ANAEROBIC CULTURE TUBE.

The tube is an ordinary culture tube of rather large size. The culture medium, *e*, is inoculated, the cotton plug, *d*, while at the top of the tube, is cut even with the glass and held in the flame until thoroughly browned, fully to sterilize it, and is then pushed down into the tube with a sterile glass rod. A cork, *c*, with two perforations, through which pass the L-shaped tubes, *a*, is fitted to the mouth of the test-tube and sealed with wax at *b*. Hydrogen gas is now passed through the apparatus for an hour or so, depending upon the size of the tube, until all the air is displaced; the entrance and exit tubes are then sealed at *a' a'* by fusing the glass. The advantage of this simple method is that any tube can be used with any of the common media in use in the laboratory.

side through the L-shaped piece. The author has fancied that the exclusion of air, when using hydrogen, was facilitated by attaching to the L-shaped piece a soft-rubber tube extending to the bottom of the apparatus; as air is much heavier than hydrogen, this device causes the gas admitted through the opposite tubulature to displace the air more rapidly. The method devised by

Sternberg is explained in the legend beneath figure 66. A more recent appliance for excluding the air without the use of hydrogen or carbon dioxid is that devised by Wright. Its form and method of application are indicated in figure 67.

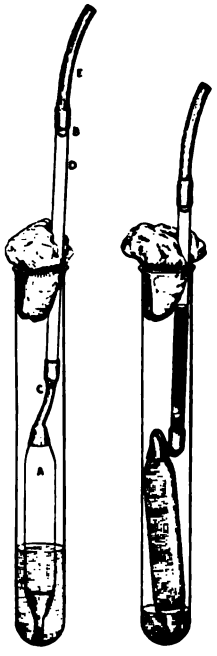


FIG. 67.—WRIGHT'S METHOD FOR ANAEROBIC CULTIVATION IN LIQUID MEDIA.

A. Spindle-shaped glass tube, at the lower end of which is attached a short piece of rubber tubing (lower B). C. Rubber tubing connecting upper end of A with lower end of D. D. Glass tube stoppered with cotton at upper B, and continued upward by the rubber tube E. For use, the apparatus is prepared as shown on the left, sterilized by steam, and may be kept in stock. Before inoculation the medium in the tube is boiled to drive off absorbed gas, cooled, and inoculated. Suction is applied to the rubber tube E, drawing the contained fluid upward to point indicated in drawing on the right; the tube is then thrust downward, kinking the rubber tube C, and in a similar manner closing the rubber tube at the lower end of A. It is claimed that this apparatus affords a ready method of securing, at the same time, both aerobic and anaerobic cultures in the one tube.

Hanging-drop Cultures for the Demonstration of Motility.—If a drop of liquid culture be placed on a slide and covered in the usual manner, examination with a high power will usually demonstrate the motility of an organism. This crude method is not accurate, as heat currents always occur in fluids under a cover-glass, and may mislead the observer. For demonstrating motility the drop-culture slide is used. This consists of a thick slide of the same dimensions as the ordinary microscope slide,

with a concavity ground in its center. A clean cover-glass is grasped in the forceps and is passed through the gas-flame to sterilize it. The concave slide is prepared in the same way, allowed to cool, and around the concavity is painted a thin line of any nonvolatile oil—ordinary sperm oil, vaselin, or, when the slide is to be incubated, paraffin or oleum theobroma liquefied by gentle heat. A droplet of the culture in bouillon or Dunham's solution is placed in the center of the cover-glass, which is then inverted over the hollow slide, care being taken that the droplet is very small,—not larger than a small pinhead, so that it will not sway from side to side,—and that it does not come in contact with the slide at any point. With the stage of the microscope perfectly horizontal, the droplet is carefully focused upon. The moving bacteria can be easily seen, provided the illumination is satisfactory; the iris diaphragm should be closed to admit but little light, otherwise the field will be so flooded with light that the small, colorless bodies—the bacteria—may escape detection. It is often advisable to center the drop with a low power—say, a ½-inch or ⅔-inch objective—before attempting

FIG. 68.—DROP-CULTURE SLIDE.
(75 × 25 mm., of polished plate glass, with a cavity 18 mm. in diameter.)

to focus with a high power. If the organism is growing on a solid medium, a small part of the culture is mixed with the bouillon or Dunham's solution on a sterile cover, and the hanging drop is prepared from the mixture.

The "hanging-drop culture"—as such the foregoing is known—may be incubated and kept under observation for a long time if care is used to avoid infection during its preparation and to exclude bacteria by a perfect oil seal. By observation in the incubator, bacteria can be seen dividing, yeasts watched while forming and throwing off buds, and other observations made. (See Widal's test, p. 112.)

During the growth of many bacteria, bodies are elaborated that change the reaction of the culture medium. This test is applied by adding an indicator to the fluid, or other medium, and observing whether the color of the indicator changes. The two indicators most commonly used are litmus and phenolphthalein; the former is kept in stock as a tincture, and the latter as a 0.1 per cent. solution of the salt in fifty per cent. alcohol. To apply the test, a number of tubes of culture media—milk, bouillon, or, what is best of all, Dunham's solution—are prepared; although

much less suitable, solid culture media, such as gelatin, agar or potato, may be used. In bulk, some of the medium—enough to fill several test-tubes of the size intended for use—has added to it enough of the indicator to show, faintly but clearly, the reaction; one part of the medium should be but faintly acid, very dilute acetic acid being used to acidify; another portion should be rendered faintly alkaline by the use of one per cent. caustic potash, while a third is neutral. With great care sterile media may be sensitized without subsequent sterilization; as a rule, however, after sensitizing it will be necessary to resterilize the test medium. The same quantity should be in each tube. A number of tubes belonging to each series are inoculated with the germ in question, and several are left as test or control reserves. In the course of a few days, often in less than twenty-four hours, it will be observed that the reaction of the two series is changing. If the germ produces an alkaline reaction, the neutral series evinces the change first, followed by the acid series becoming less markedly acid and, in some instances, eventually manifesting a clearly defined alkaline reaction. The alkaline series may show a slight intensification of the alkaline reaction or may not change at all. The control tubes should remain constant. If the organism produces an acid, the reaction just given will be reversed.

Rosolic acid is also used as an indicator; the stock solution is prepared by adding 0.5 gm. of the acid to 100 c.c. of eighty per cent. alcohol. Its use is the same as the foregoing; it pales when acid, intensifies its rose-color when alkaline.

Indol.—Among the chemic tests applied for the identification of bacteria is that for indol. Several tubes are charged with seven cubic centimeters of Dunham's solution, sterilized, and three or four inoculated with the germ under investigation, and twice the number reserved for controls. After twenty-four hours add to one of the controls ten drops of chemically pure sulphuric acid, and to another one cubic centimeter of a sodium nitrite solution, freshly prepared, and made by dissolving one gram of chemically pure sodium nitrite in 10,000 c.c. of ammonia-free water. To the second tube also add ten drops of sulphuric acid. Both tubes should be watched for fifteen or twenty minutes; no color should develop, as they contained no indol. To one of the inoculated tubes add the sulphuric acid, and if in from ten to twenty minutes no reaction occurs, add the sodium nitrite solution, as previously directed; if indol be present, a distinct rose-color appears. Occasionally the rose-color may appear without the addition of the sodium nitrite, in which case the organism

has produced not only indol, but also a reducing agent, commonly a salt of nitrous acid.

Thermic Disinfection.—Each organism thrives best at a certain temperature, known as its *optimum temperature*. Variations above or below the most favorable degree of heat influence the growth of the germ in question. The lowest temperature at which growth takes place is called the *minimum temperature;* the highest, the *maximum temperature*. The three thermal points are rarely the same for any two organisms, and hence constitute important tests in the identification of a germ under investigation. The *thermal death-point* is that degree of heat destroying the life of a germ; a knowledge of the point at which the organism is destroyed also aids in the differentiation of bacteria. The thermal death-point is not constant for the same microbe under all conditions, varying, in some cases, with the age of the organism, the presence or absence of moisture, etc. Again, moist heat is usually destructive to bacteria at a lower temperature than dry heat; and moist heat under pressure (superheated steam) more penetrating and more rapidly fatal than dry heat at the same temperature.

In order to determine the thermal death-point of a given organism all the foregoing factors must be borne in mind, as well as the length of time of exposure. The latter also varies with the conditions under which the test is made. A temperature of 70° C., moist or dry, and continued for one or two hours, may be, to a given organism, as certainly fatal as 100° C. with an exposure of ten minutes. The thermal death-point in the presence of moist heat is commonly determined by exposure of bouillon cultures, infected material, or dried threads—prepared as described under Chemic Disinfection (see below)—to different temperatures and for different lengths of time in the steam sterilizer (Fig. 52, p. 83) or in the autoclave (Fig. 54, p. 85). In making the test with dry heat the hot-air sterilizer (Fig. 49, p. 81) is used, and previously dried infected materials, especially dried threads, make the best test-objects. After exposure of the infected material to the heat, inoculations are made upon suitable culture media, and the tubes are incubated and kept under observation a sufficient time for the development of any undestroyed germs. The thermal death-point of an organism may be determined even before its successful cultivation. Such an experiment is permissible only when we can not successfully cultivate the germ. In order to make the test we must be able to infect an animal. Material that is known to contain the organism in question is subjected to heat, and, after definite exposures, is

inoculated into susceptible animals. If disinfection has been complete, the inoculated animals escape. A source of error lies in the well-known fact that the pathogenicity of an organism may be lowered without of necessity destroying its viability; if, however, the experiment has rendered the germ no longer capable of inducing disease, its infectivity is removed, and therefore disinfection, in the theoretic sense, has been secured.

Theoretically, there should be two death-points—a maximum and a minimum; but experience has satisfactorily proved that there is at present available no temperature sufficiently low to act as a disinfectant upon which it is possible to rely. Reduction below zero commonly determines only a stage of inactivity that ends with return of the organism to conditions again compatible with growth.

Chemic Disinfection.—In addition to the influence of thermic changes on bacteria, it is necessary to study the effect of disinfectants belonging to the chemic group. The relation of other physical agents than heat may also be studied: *e. g.*, drying, light, and electricity. In studying disinfectants, solutions are to be used almost exclusively; insoluble disinfectants are of more than doubtful value. Again, a culture medium must be used that does not alter the chemical in question. Thus, if, in the study of corrosive sublimate, a culture medium rich in albumin or strongly alkaline be used, the mercurial is instantly decomposed when it comes in contact with the culture medium, and, it may be, before it has had time to act upon the bacteria. Having found the desired culture medium, the next point to determine is the exact point at which the body under investigation ceases to be antiseptic: that is, inhibits the growth without of necessity destroying the life of the bacteria. For this purpose a series of tubes of culture media are prepared containing the antiseptic in varying quantities. These are best prepared, if possible, by taking 50 or 100 tubes of the medium it is desired to use, sterilized in the usual way: To ten of these enough of the agent is added to make the strength ten per cent.; to another ten, enough to make the strength five per cent.; to another ten, four per cent.; and so on, covering various percentages.

All these tubes are inoculated with the germ that it is proposed to use for the test. A series will be found beyond which the agent is in such dilution as not to interfere with the growth and above which the dilution may be antiseptic without of necessity destroying the germ—inhibits growth but does not disinfect. The strength at which disinfection—that is, destruction of reproductive power—occurs may be approximately inferred by dilut-

ing with the same sterile culture medium the tubes in which no growth has evinced itself, so that the proportion of the disinfectant in the dilution shall be less than that already found to not inhibit growth. After this dilution the bacteria that have not been destroyed develop, showing in what strength disinfection has been complete. This has, however, taken so much time—probably days—that doubt may still exist as to the rapidity with which the agent in question acts ; and as the time required by a given solution to destroy viability is important, we must determine the rapidity of action and the strength necessary to use to be practically available. For this purpose a number of methods have been suggested, all of which are open to certain sources of error.

To a number of cultures in a liquid medium the agent in question is added, so as to make the percentage such as has been found in the previous test to be destructive ; the added solution is thoroughly mixed with the culture, from which inoculations are made at intervals of minutes for as long as an hour. The removal must be made into tubes containing sufficient of the medium to dilute the material carried over beyond the strength already shown to have an inhibitory action, so that any undestroyed bacteria may be free to develop.

FIG. 69.—SMALL INCUBATOR SUFFICIENTLY LARGE FOR INDIVIDUAL WORK.

The source of error by this method lies in the clumping of the germs in the original tube ; if grouped in clumps, the agent may not have penetrated the clumps. Penetration is a most important point, for without this power a disinfectant is of little practical value ; as, in all purposes for which germicides are used, a certain degree of penetration is necessary, this apparant objection is not without its good side. To get rid of the clumps, cultures are made in a medium containing fine quartz sand ; this is shaken up in the culture and the culture filtered through glass wool and the filtrate used for the test. Tubes containing the sand may have mixed with them growing cultures containing no

sand. Again, threads of silk from two centimeters to six centimeters in length may be placed in tubes of liquid culture media, the tubes sterilized as usual, and, when sterile, infected with the germ that it is intended to use for the test. When the culture is well grown, it is shaken, the threads are withdrawn, and may be used as test bodies to disinfect; they may be first dried in sterile dishes or they may be used moist. A source of error lies in the quantity of the disinfectant that the thread may convey into the tube into which it is transplanted after treatment with the disinfectant. In some cases this may be partly avoided by washing the thread in sterile water or in some solution, or by exposing it to a vapor, which, by chemic action, converts the disinfectant into an insoluble or inactive compound. Thus, threads which have been in corrosive sublimate solutions may be exposed to ammonium sulphid vapor, the solution converting the mercurial into an insoluble and inactive sulphid.

It will be noted that one of the essential elements is to make the transplantation, after treating the thread or culture with the disinfectant, into such a quantity of new noninfected medium as to assure a dilution beyond the inhibiting point, which may be due to any of the antiseptic carried over on the thread or on the platinum loop. Thus, if a thread has been exposed to a solution of an agent,—say, in the strength of 1 : 100,—and the inhibiting action is present in a solution having a strength of 1 : 1000, it will be necessary to carry the thread into a medium having a minimum bulk, in order to be safe, of at least 100 times the quantity carried over on the thread, in order to assure such dilution as not to preclude the disinfectant preventing growth of any undestroyed organism.

In testing gases, threads, cultures, and other infected materials are exposed in a closed chamber, such as a bell-jar, to the gas, either pure or with a known dilution of air.

In addition to the foregoing system of tests, so-called *practical tests* are made. A known quantity of pus, blood, sputum, or feces is mixed with a known quantity of the disinfectant, and cultures are made at intervals of from two to five minutes. Varying strengths of the disinfectant are used with exposure for different lengths of time; in this way purely laboratory experiments are controlled by what are considered practical methods.

Again, animals may be inoculated with cultures or threads that have been exposed to disinfectants. In the latter case it is to be remembered that in rare instances the pathogenicity may be reduced without the germ being destroyed.

To study the pathogenesis of an organism, **inoculation of**

animals is necessary. The animals most used are rabbits, guinea-pigs, rats, and mice. The absolute requisite to success is careful asepsis at every stage of the process, and during the postmortem if the animal dies. If the disease or a disease is produced, and it is desired to obtain cultures, they must be secured with the same strict attention to detail.

All instruments used in the various stages of inoculation, examination during life, or postmortem, should be sterilized by heat: preferably dry, although moist heat may be used. Chemic disinfection must be regarded with suspicion, although syringes may be sterilized in a five per cent. solution of carbolic acid allowed to act for one or, better, two hours, during which time the solution should be kept warm. Pure formalin may be used on instruments. No matter what chemic body is used, it must be thoroughly removed by washing in sterile water before proceeding with the operation. The hands of the operator and of

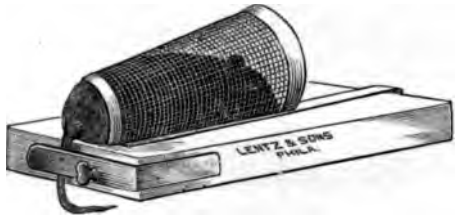


FIG. 70.—APPARATUS FOR HOLDING A MOUSE OR RAT FOR INOCULATION. (Devised by Dr. Lydia Rabinowitsch and Dr. Voges.)
The inoculation is usually made just over the root of the tail.

the assistants, and the table upon which the operation is to be conducted, should be washed with soap and water as hot as can be tolerated, followed by alcohol, ether, and finally corrosive sublimate solution (1 part of the salt dissolved in 1000 parts of normal salt solution), which should be allowed to act several minutes, followed by thorough washing in sterile water.

Of the many methods for inoculating an animal, the following will be found useful:

1. *Subcutaneous inoculation* is the one most frequently used. The site of the contemplated operation is shaved, washed with soap and water, water, alcohol, ether, alcohol, and corrosive sublimate solution (1 : 1000), and the last removed by thorough washing with sterile water. Between the scapulæ and near the tail are the most convenient sites for inoculation, but any point where the tissues are lax will answer the purpose.

The skin is stretched and made tense, an incision or pocket is

made in the tissues about five millimeters to ten millimeters in length and correspondingly deep under the skin; into the pocket so made a loop of the growing organism or suspected material is introduced, after which a layer of sterile cotton is laid over the wound and a thick coating of collodion applied; in a few minutes this will dry; the animal is then liberated and kept with an uninoculated animal known as the control. Subcutaneous injection of bacteria, suspended in sterile water or bouillon, may be resorted to as directed for intraperitoneal inoculation.

2. Intraperitoneal injections are made by preparing the animal as before. A syringe graduated in cubic centimeters is necessary for this method. The skin of the abdominal wall—the site of the operation—is prepared as previously explained, grasped by an attendant, and raised as a fold, into which the needle is introduced and forced onward into the peritoneum, then partly

FIG. 71.—KOCH'S SYRINGE FOR HYPODERMIC, INTRAPERITONEAL, AND OTHER INJECTION METHODS FOR INOCULATING ANIMALS; THE CAPACITY SHOULD BE ABOUT TWO CUBIC CENTIMETERS.

withdrawn to make sure it is free in the peritoneal cavity. The syringe is now attached, a given quantity of bouillon culture is introduced, and the wound is sealed as before.

3. Intravenous inoculation is made directly into the vein; the most convenient veins are those of the rabbit's ear. The overlying skin is prepared as already directed, and an incision is made down upon, but not into, the vein; when the vein is thoroughly exposed, the needle of the hypodermic syringe is thrust into the vein in the line of the blood-current, and the contents of the syringe are slowly injected. Great care must be used to see that no air enters the vein, and that no clumps or other solid material that might cause embolism are thrown into the blood.

4. Inoculation into the Anterior Chamber of the Eye.—Anesthetize the cornea by cocain, wash with sterile water, perforate the cornea at the scleral margin with a hypodermic needle, through which the material is injected; the quantity should be

very small—scarcely a half drop; otherwise a disturbing tension is created that greatly modifies the result of the operation.

5. Tissue Implantation.—Sometimes a small piece of pathologic tissue is used for inoculating (as in glanders and tuberculosis). The implantation may be made into the subcutaneous tissues or serous cavities. In the first instance a pocket is prepared as already directed for subcutaneous inoculation, into which the block of tissue (which should not be larger than from two to five millimeters cube—the smaller the better) is implanted, the wound sealed, if necessary, sutured, and covered as already directed. For transplantation into a serous cavity, the peritoneum is usually selected. Under the strictest asepsis the cavity is opened, the tissue dropped in, and the opening closed. In some instances, in order to assure vascularization, a tip of the omentum is brought out, the block of tissue rolled in the serous membrane, and the roll secured by a stitch. The foregoing methods demand the use of a piece of tissue of macroscopic proportions, and leave a wound through which accidental infection

FIG. 72.—SPATULA USED FOR SHARING THE SURFACES OF ORGANS BEFORE MAKING INCISIONS INTO THEIR INTERIORS FOR OBTAINING CULTURE MATERIAL.

may occur. In many instances the difficulties just indicated may be evaded by rubbing up the material in a sterile glass mortar with a small quantity of sterilized water. Unless there is an unusual amount of connective tissue, the maceration may be sufficient to permit of injection through a comparatively large hypodermic needle. When there is reason to believe that the water may act deleteriously, some other menstruum, such as normal salt solution or blood-serum, may be used.

After-treatment of the Animal.—Medication of all kinds should be avoided; overcome the immediate shock by the gentlest handling of the animal, abundance of fresh air, and warmth. It should be treated exactly as a control (an uninoculated animal of the same species), but, as a rule, should be in a cage or inclosure by itself; otherwise the control may injure the inoculated animal.

The Postmortem.—If the animal dies, the body should at once be washed with soap and water and with water and alcohol, and immersed in 1 : 1000 corrosive sublimate solution, followed by washing with sterile water. A postmortem is made under strict

asepsis. As soon as the heart is exposed, a spot on the surface of the right auricle is seared by heating a spatula and laying it down on the surface of the organ; this thoroughly disinfects the surface. Thrust a sterile inoculating needle into the auricle, and move it through the blood backward and forward until a drop emerges along the side of the needle, when it is withdrawn and a tube of medium inoculated, which may be at once poured into a plate. (See Plate Methods.) This operation is repeated for each cavity of the heart and for all important organs of the body. Pieces of tissue are hardened, either in absolute alcohol or corrosive sublimate, and prepared for sections in the usual manner. (See Killing and Fixing of Tissues, p. 48; also Staining of Bacteria, p. 93.)

Method of Preparing Toxins and Antitoxins.—The preparation of the diphtheria antitoxin is as follows:

As the bacilli develop their toxins most rapidly in the presence of a moist current of air, a flat-bottomed vessel with two lateral tubes is charged with bouillon containing two per cent. of peptone. After thorough sterilization, inoculate with fresh virulent cultures of the diphtheria bacillus. Incubate at 37° C. until development begins, and then force through the lateral tubes a current of moist air.* A sufficient quantity of toxin will be developed in from three to four weeks. Filter through a Pasteur-Chamberlain filter, preserve in well-stoppered bottles, and keep in a dark place. In doses of 0.1 c.c. this filtrate should kill a guinea-pig weighing 500 grams in from forty-eight to sixty hours. For the purpose of immunizing animals, this fluid is in many cases too strong for the first injections, and should be diluted with one-fourth its volume of Gram's solution. Roux and Vaillard have determined that the toxin is much less dangerous when combined with iodin. A medium-sized rabbit should receive an injection of 0.5 c.c. The injection is repeated in a few days, and thus continued for several weeks. With each successive injection the proportion of Gram's solution should be diminished, and the dose slightly increased until the pure toxin is reached. After injection of the toxin the animal not infrequently manifests a slight rise in temperature, with accelerated pulse, and sometimes an evident malaise. A second injection should not be given until all symptoms of the previous injection have disappeared. The amount of toxin is gradually increased until the animal bears without inconvenience a dose equal to 100

* The aeration of the flask is no longer practised, experience having shown that it is not demanded.

minimum fatal doses. If during this time a loss in body-weight becomes manifest, the injections should be discontinued, or there may be induced a fatal cachexia.

Dogs, sheep, goats, horses, and cows may by this procedure be rendered immune. The milk of immune animals may offer an important source of the antitoxin. The horse is easily immunized, and will supply large quantities of the antidiphtheric serum. Horses bear proportionately large doses better than other animals, and but a transient fever will succeed a dose of from two to five cubic centimeters of a strong toxin.

FIG. 73.—STERNBERG'S FLASK, USED FOR COLLECTING FLUIDS, WATER, ETC., AND FOR HOLDING CULTURES IN LIQUID CULTURE MEDIA.

Before using, it is sterilized in the hot-air oven. To fill, the point is broken off and the bulb is heated, thus expelling some of the contained air; the point is then thrust into the fluid, and, as the bulb cools, the fluid rises into it; when the desired quantity is drawn into the bulb, the point is sealed in a gas-flame. Certain brands of antitoxin are now dispensed in bulbs similar to the one here illustrated.

FIG. 74.—KITASATO'S FILTER.

The material to be filtered is placed in the upper bulb, which is connected with the central bougie of unglazed porcelain. The point of connection between the receiving chamber and the filter bougie is covered by a rubber cork, which fits very tightly into the neck of the flask. Through the lateral arm of the flask, extending out to the right, the air is exhausted from the interior. In this way filtration, ordinarily slow, may be accelerated by air pressure. The filter is mostly used for separating germs from their toxins.

Antitoxin is obtained from the animal by bleeding under the strictest conditions of asepsis, receiving the blood through a cannula into a sterile jar, flask, or other container, as already directed for the preparation of blood-serum for culture purposes. The obtained serum may be preserved by the addition of tricresol, thymol, carbolic acid, camphor, etc. It should be sterile, and if care has been taken to exclude contamination during the various stages in its preparation, the addition of a preservative will be unnecessary.

In order to estimate the *strength of an antitoxin*, we must first know the minimum fatal dose of a toxin. This information is obtained by selecting a number of guinea-pigs, each of which weighs 250 gm., and by injecting subcutaneously different quantities of the toxin under investigation. The minimum fatal dose is that which kills a guinea-pig weighing 250 gm. on the fourth or fifth day. In order to exclude possible error, arising from unusual susceptibility or insusceptibility of the animal, a number of injections should be made and a fairly uniform result finally attained.

The strength of the antitoxin present in the serum, obtained as previously described, is expressed in *immunity units*. An immunity unit is ten times the quantity of antitoxin necessary to protect a guinea-pig weighing 250 gm. from ten times the minimum fatal dose of toxin. In order to determine the strength of a given serum we proceed as follows:

A number of test doses of the toxin are prepared, each containing ten times the minimum fatal dose. To each test dose is added a measured quantity of the serum in question. To one dose is added 0.01 c.c. of the serum; to another, 0.05 c.c. of the serum; to another, 0.1 c.c. of the serum; to another, 0.5 c.c.; and to still another, 1 c.c., and so on. The mixtures are now injected into guinea-pigs and the results observed. Protection implies that no swelling, rise in temperature, or evident disturbances of nutrition follows this administration. The mixture containing the smallest amount of serum and yielding this result contains 0.1 of an immunity unit. Assuming that the quantity of serum present in the test dose that yielded the foregoing result was 0.1 c.c., then 1 c.c. of such serum contains an immunity unit of the antitoxin. Antitoxin, as placed upon the market, is labeled as containing a certain number of immunity units, and the measured quantity of serum necessarily varies, as the number of units obtained are rarely exactly the same in two animals.

For the treatment of disease the antitoxin is administered subcutaneously.

Widal's Test for the Diagnosis of Typhoid Fever.*—*Culture Employed.*—The culture used in the Widal test should be

* This description of the method was abstracted by Dr. J. C. Da Costa, assistant in clinical microscopy, Jefferson Medical College, from his article in the "New York Medical Record," August 21, 1897, in which he reports an examination of over 100 cases, and also an analysis of the literature on the subject up to the date of publication. I am also indebted to Dr. Da Costa and to the publishers of the journal for permission to use the accompanying illustrations. More recent improvements in technic have been added.

taken from an agar growth that has been allowed to develop at ordinary room-temperature for at least twenty days. From this agar culture inoculations are made into tubes containing neutral beef bouillon, and these tubes, after incubation at 37.5° C. for from eighteen to twenty-four hours, are used in the test. Instead of making bouillon growths, emulsions in sterile distilled water may be used with good results by thoroughly mixing a bit of a recent agar growth with about 2.5 c.c. of sterile water in a test-tube until a uniform cloudiness appears.

The precautions previously indicated must be followed to avoid certain false or pseudo-reactions, which sometimes occur when normal blood or blood from individuals suffering from diseases other than enteric fever is added to a virulent culture of the typhoid bacillus.

Method of Conducting the Test.—The blood is obtained by puncture of a finger, and three separate drops are allowed to fall upon the surface of a perfectly clean glass slide that has been passed through a flame and cooled just before use. The glasses are permitted to dry, and are then placed in a box to await examination at a convenient time.

To one of the blood-drops a large drop of sterile distilled water is added to effect a solution of the dried blood; and while this is going on, the other preparations for the test are being made, by cleaning and sterilizing by the flame two cover-glasses and a "concave slide," to be used for the microscopic examination of the specimen.

On one of the cover-glasses six drops of the typhoid bouillon are now placed, and to this is added a large drop taken with a platinum loop from the summit of the blood solution, and the whole is thoroughly mixed together. From this mixture of blood solution and typhoid bouillon a minute quantity is now placed with a platinum needle upon the center of the second cover-glass, which is immediately inverted over a hollow-cell slide, sealed with either vaselin or cedar oil, and examined under the microscope with a 1/8-inch dry objective. (See Hanging-drop Culture, p. 101.)

Instead of the glass slide previously recommended for receiving the blood, a small piece of highly glazed paper may be substituted. Whether using the glass slide cover-glass, foil, or paper, the blood as received at the laboratory is dry, and the difficulty that at once confronts the investigator is to restore this to its original volume. It does not seem probable that accurate restoration is ever possible, and for this reason the dry method must always be liable to error, depending upon our total inability

accurately to determine the dilution that is being used. The majority of observers are in favor of a 1 : 20 dilution, and for this purpose the writer is not familiar with any method that possesses advantages over that devised by Cabot.

A drop of blood is placed in a tube or other container, and at once there are added, using the same pipet, nine drops of sterile water. This fluid is taken to the laboratory and one drop mixed with one drop of a bouillon culture of the typhoid bacillus, giving as nearly as can be obtained a dilution of 1 : 20. If not unnecessarily agitated, the corpuscular elements will lie mostly at the bottom, and the supernatant fluid may be, in a short time, clear. When the mixture has not cleared, sedimentation may be hastened by the use of the centrifuge.

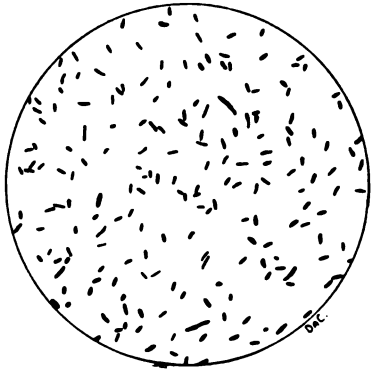


FIG. 75.—BACILLUS TYPHI ABDOMINALIS.
Hanging-drop culture, prepared as directed on page 101. The bacilli are actively motile throughout the field.

FIG. 76.—A POSITIVE REACTION.
Large clumps of motionless bacilli separated by open spaces. The few bacteria outside the clumps are devoid of motility.

Appearance of the Reaction.—If the reaction is positive, the observer will see large clumps of motionless, agglutinated bacilli, which appear as irregularly shaped islands, separated by open spaces containing, perhaps, a few isolated bacteria, whose power of propulsion is either decidedly inhibited or entirely lost.

If the reaction be negative, the bacilli will appear as actively motile rods, darting across the field in every direction, and showing no tendency to form into masses, although occasionally small clumps of the microorganisms may be noted. In negative reactions, however, clump formation never progresses to any marked degree, and motility persists, regardless of the time during which the specimen is watched. If any doubt exists as to the nature of a reaction, a "control" slide should be pre-

pared with normal blood and typhoid bouillon, for purposes of comparison. (See Figs. 76, 77, 78.)

The time required for the completion of a reaction varies, but in a general way it may be said that typhoid blood will cause definite clumping and loss of motility of the typhoid bacilli within thirty minutes in the great majority of instances. In some cases a much longer time will be necessary before a correct interpretation of the test can be arrived at. *A reaction may*

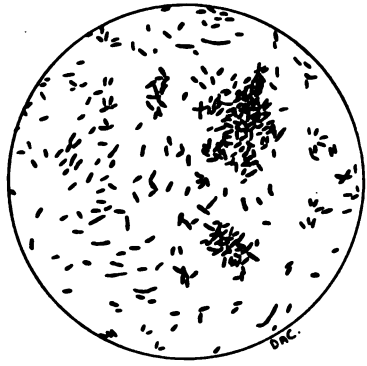


FIG. 77.—A PSEUDO-REACTION.
A few small clumps of bacilli having impaired motility. Persistent motility of the bacteria in other parts of the field occurs.

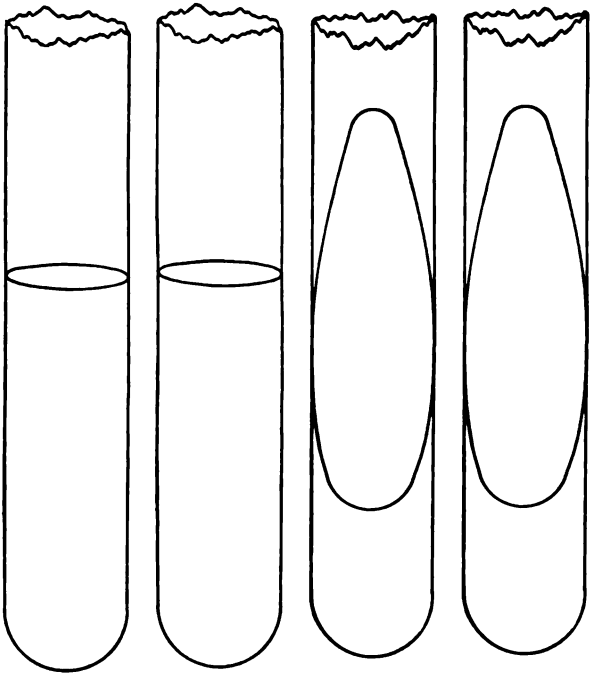
not be classed as positive unless both clump formation and loss of motility coexist, and those reactions in which either of the phenomena are wanting may not be called typical in any sense.

Systematic Records.—In order to render comparable studies made by different investigators, as well as for comparison of the characteristics of different bacteria, it becomes necessary to select some definite order of study and a method by which accurate records may be kept. The method which follows presents nothing original, and is that in use in the laboratories under the author's supervision. The entire blank, as well as the outline drawings of culture tubes (*b*, *c*, *d*, *e*, table on p. 116), are supplied to the student, and on these blanks he draws in black, or better in color, the cultural peculiarities of the microorganism under investigation. For noting the changes observed in the culture from day to day the drawings made each day are kept, and the entire series clamped or gummed together for filing. The table not only affords a satisfactory means for recording the characteristics of an organism, but also indicates what data should be worked out, and the usual sequence in which the results attained are recorded.

TABLE ILLUSTRATING METHOD OF RECORDING THE PRINCIPAL CHARACTERISTICS OF AN ORGANISM.

(A) Where found.
(B) Morphology. (*a*) Form, (*b*) size, (*c*) arrangement.
(C) Stains. Reaction to Gram's method of staining.
(D) Motility { (1) Flagellate. (2) Nonflagellate.
(E) Method of reproduction.
(F) Products of growth: (*a*) Acids, (*b*) alkalies, (*c*) odor, (*d*) color, (*e*) gases, (*f*) enzyme, (*g*) indol, (*h*) toxin, (*i*) other chemicobiologic reaction or product.
(G) Characters of growth on: (*a*) Plates.

MAKE DRAWING.



(*b*) BOUILLON. (*c*) GELATIN. (*d*) AGAR. (*e*) BLOOD-SERUM. (*f*) SPECIAL MEDIUM.

(H) (*a*) Aerobic, (*b*) anaerobic { (1) Facultative. (2) Obligate.

(I) Reaction of medium best adapted to its growth. Reaction of cultures in milk.

(J) (*a*) Optimum temperature, (*b*) thermal death-point { (1) Moist heat. (2) Dry heat.

(K) Influence of antiseptics and disinfectants.

(L) Pathogenesis.

(M) Immunity, method of securing, duration, blood characteristics in and influence of blood-serum of immune animal on the organism.

(N) Remarks: Peculiarities not embraced in foregoing form.

CHAPTER IV.

MICROSCOPIC EXAMINATION OF URINE.

Collection of Sample.—The amount of urine necessary for the examination will depend somewhat upon the object of the examination and upon the condition of the urine. In most instances at least eight ounces should be submitted to the examiner. It is best that it be collected in a perfectly clean bottle and delivered at once. When bacteriologic examination is desired, the container should have been disinfected, as already directed on page 80. When an examination is to be made for tubercle bacilli, or, indeed, in any bacteriologic examination, it is desirable to have all parts of the external genital organs that are likely to come in contact with the urine cleansed, or, what is even better, the urine may be drawn with a thoroughly cleansed catheter. Smegma bacilli are so abundant in the external genital organs of the female that it is best to use extra precautions, and, if possible, to remove the urine by means of a glass catheter that has been sterilized in a hot-air oven at a sufficiently high temperature to carbonize any bacteria that may be upon or within it. As soon as received, the urine should be sedimented. This may be accomplished by permitting it to stand in a conic glass, such as is shown in figure 79. A better and more convenient means for securing sedimentation is by the centrifuge. Of the various forms of centrifuge, those in which the power is supplied by the hand or turbine are to be preferred.

Method of Conducting the Examination.—As soon as the sediment has been secured by either of the methods previously indicated, a sterile pipet, closed by the finger at the upper end, is cautiously introduced through the supernatant fluid into the sediment, the finger is cautiously drawn to one side, permitting a few drops of sediment to enter. The finger is then held tightly over the pipet, which is at once withdrawn from the urine. The fluid on the outside of the pipet is then removed with a cloth or paper, and, holding the pipet perpendicularly, a small drop is placed on the slide and a cover-glass applied. Drain off excess of fluid with blotting-paper, and examine with ⅔ of an inch and ¼ or ⅙ of an inch objectives.

Preservation of the urine may be aided by adding a crystal of thymol, camphor, or menthol. If it be desired to preserve the sediment, this is best accomplished by carefully decanting the supernatant fluid and adding an equal quantity of a saturated aqueous solution of potassium acetate, allowing this to remain forty-eight hours, again decanting, and adding fresh acetate solution. After repeating this three times, no difficulty will be found in preserving casts, blood, epithelium, etc., present in the sediment. Casts may be preserved indefinitely in chloral, provided they have been washed according to the methods just indicated. The chloral solution should have a strength of about twenty grains to the ounce of water, and should exceed in volume one hundred times the volume of the sediment to be preserved.

FIG. 78.—WATER CENTRIFUGE.

The number of revolutions depends on the water pressure and on the size of the supply pipe. A pipe at least ⅜ of an inch should be used, and the larger the better. The ordinary city pressure is about 25 pounds; with ⅜-inch pipe this will give 1200 revolutions a minute; 30 pounds will give 1400; 35 pounds, 1500. By enlarging the supply pipe the speed rapidly increases. A thousand revolutions a minute are sufficient for urine sedimentation. Tubes A and B hold one ounce each.

ORGANIZED SEDIMENT (*Cellular Constituents*).—*Red Blood-corpuscles.*—When these corpuscles occur in large numbers and

in good condition without being intimately blended with the urine, they are usually from the bladder or urethra; but when they do not form a red sediment after many hours' standing, and have lost their coloring-matter and appear as pale yellow, washed-out rings (phantom corpuscles of Traube), especially if associated with blood-casts, the hemorrhage has probably occurred in the substance of the kidney, renal pelvis, or ureters.

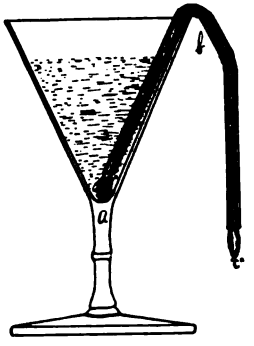


FIG. 79.—CONIC GLASS SUITABLE FOR THE SEDIMENTATION OF URINE.—(*Coplin and Bevan.*)

In position is shown a candle-wick filter for securing urinary sediment. The filter consists of a glass tube so bent that the longer arm is outside and opens below the level of the bottom of the conic glass. Through the bent glass tube are drawn a few strands of candle-wick to fill the tube rather tightly. By capillarity the urine rises in the bent tube and eventually flows over; in so doing it deposits all the sediment on that end of the candle-wick which is at the bottom of the glass. This is gently brushed over a number of slides, cover-glasses are applied, and the slides examined at once.

FIG. 80.—CENTRIFUGE WITH HEMATOCRIT ATTACHMENT.

The attachment for sedimenting liquids such as urine is shown in position for use. This may be lifted off and the hematocrit attachment shown in the upper part of the figure substituted in the place of sedimenting attachment shown in position. There are two gears, one for sedimenting blood, known as the high gear, and which gives 10,000 to 14,000 revolutions a minute; the lower gear, for sedimenting urine, giving from 2500 to 4000 revolutions a minute. The crank is easily transferred from one gear to the other.

Pus.—Urine containing pus in any quantity is always turbid when voided, and shows decided reaction for albumin if the quantity of pus be at all large. Pus-corpuscles are nearly twice the size of red blood-corpuscles, and appear as pale, circular, granular discs with several nuclei, and are practically identical with mucus corpuscles, white blood-corpuscles, and lymph-cells.

They may show ameboid movements when examined in the fresh state, but, as seen in urinary sediment, their protoplasm is coagulated into coarse granules.

Epithelium.—(Make drawings of different forms.)

Squamous epithelium.

Transition epithelium.

Epithelium from bladder.

Urinary Casts.

I. Those consisting of cells.

II. Those that consist of the products of cellular change.

III. Hyaline casts.

Examine with ¼-inch or ⅙-inch objective and make drawings of—

Blood-casts,
Epithelial casts,
Granular casts,
Waxy casts,
Fatty casts,
Hyaline casts,
Pus-casts,
Bacterial casts,
Cylindroids,
False casts, composed of urates or crystals,
Casts from seminal tubes.

Spermatozoa are thread-like bodies, 50 μ long, provided with a head and a long, tapering, tail-like extremity.

Their constant deposit indicates spermatorrhea. They are easily identified in urinary sediment, or may be stained as follows: Spread a thin layer of the sediment on a clean cover-glass; dry without heat; stain in carbolfuchsin for two seconds; wash in water; *dry*, and mount in balsam.

Nonpathogenic Fungi:

Molds, or large segmented rods.

Yeast plants (saccharomyces urinæ and other yeasts) are arranged in bead-like forms with budding cells attached.

Bacteria of decomposition.

Pathogenic Fungi.—*Tubercle Bacilli.*—In all cases of purulent urine accompanied by anemia, wasting, and evening rise in temperature, the urinary sediment should be examined for tubercle bacilli.

Purulent deposits of tuberculous urine should be treated the same as sputum in searching for tubercle bacilli. The centrifuge aids materially in this examination. Experience shows that residual urine drawn with a catheter after the patient has appar-

ently voided all the contents of the bladder is more likely to contain tubercle bacilli than the tidal urine.* (For method of demonstration see Tubercle Bacilli.)

Gonococcus (Neisser).—Minute, roll-shaped diplococcus found in urine containing gonorrheal pus. (For method of staining and description see article on Bacteriology.)

Distoma Hæmatobium.—The eggs of this parasite, about 125 μ in length, are oval or flask-shaped, and are found accompanied by blood-cells and pus.

Filaria Sanguinis Hominis.—The embryos are occasionally found in chyluria. (See Animal Parasites.)

UNORGANIZED SEDIMENT (*Crystalline and Amorphous*).

Sediment of Acid Urine.—(Examine and draw the various crystals.)

Uric acid (whetstone crystals).
Oxalate of lime (envelop crystals).
Hippuric acid.
Urate of soda.
Tyrosin and leucin.
Soaps of lime and magnesium.
Amorphous deposits.
Urates.
Brown and yellow concretions.

Sediment from Alkaline Urine.

Triple phosphates (coffin-lid crystals).
Urates of Ammonium (hedgehog crystals).
Indigo.
Cholesterin.
Amorphous deposits.
Phosphate of lime.
Carbonate of lime.

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* Bryson, American Association of Genito-urinary Surgeons, May 6, 1897.

ILLUSTRATIONS OF VARIOUS URINARY SEDIMENTS.*

FIG. 81.—PHANTOM AND DISTORTED RED BLOOD-CELLS FOUND IN URINE, MOST COMMONLY THAT OF RENAL HEMATURIA. —(*Landois.*)

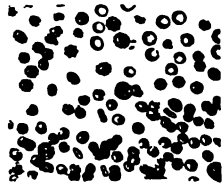

FIG. 82.—BLOOD-CELLS IN THE URINE.—(*Gould.*)

The cells that appear almost normal could not have been subjected to the action of the urine but for a short time.

FIG. 83.—BLOOD-CELLS IN THE URINE, LYMPH-CORPUSCLES, LEUKOCYTES OR PUS-CELLS, AND CRYSTALS OF TRIPLE PHOSPHATE. × 350 diameters. —(*Landois.*)

FIG. 84. — PUS-CELLS IN URINE.—(*Gould.*)

Many are irregular or fragment forms.

FIG. 85.—EPITHELIUM FROM THE CONDUCTING PART OF THE URINARY APPARATUS, MOSTLY FROM THE BLADDER.

Note in the upper left-hand part of the figure the cells that resemble renal epithelium.

FIG. 86.—RENAL EPITHELIUM.

The four cells below and to the left are fatty. This form of epithelium will be found on casts and free in the urine. It will be noted, however, that it so closely resembles epithelium from one layer of the conducting apparatus that the diagnosis of free renal epithelium may be open to criticism. See figure 85, epithelium from the bladder.

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* Experience has convinced the writer that the best way to learn to recognize the various urinary sediments is to take as good an illustration, or series of illustrations, as can be secured, and work at the microscope with the illustrations at hand until able to recognize all the ordinary forms.

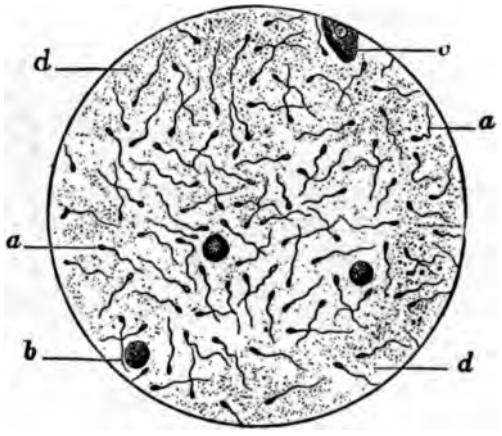

FIG. 87.—SEMINAL ELEMENTS, SOME OF WHICH MAY BE FOUND IN URINE. *a, a.* Spermatozoa. *b.* Seminal cells. *c.* Epithelium. *d, d.* Seminal granules.

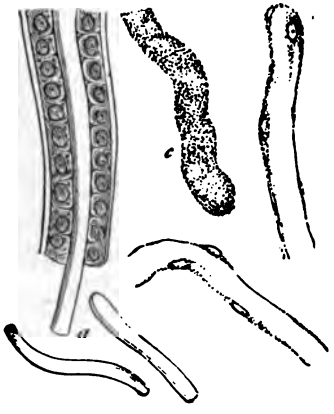

FIG. 88.—ILLUSTRATING THE FORMATION OF CASTS.—(*Rindfleisch.*)

a. Hyaline cast in place. If it comes away bringing nothing with it, it will remain a hyaline cast. If it brings epithelium, it will be an epithelial cast; if the epithelium is granular, it will be a granular cast; if fatty, a fatty cast. *c.* Granular cast. The two casts in the lower corner, and to the left, are hyaline; the remaining casts are largely hyaline, but bear a few epithelial cells.

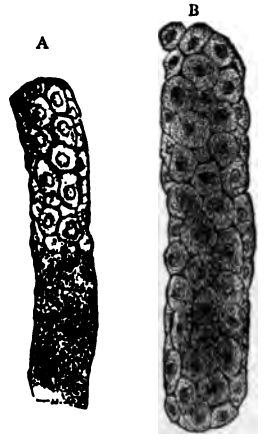

FIG. 89.—EPITHELIAL CASTS.—(*Landois.*)

A. Epithelial cast, the lower end of which is coarsely granular. B. Epithelial cast in which the epithelial cells, though themselves granular, have not broken up.

FIG. 90. — BLOOD-CELLS AND BLOOD-CAST.—(*Landois.*)

FIG. 91.

A. Hyaline cast. *B*. Hyaline cast with a few attached leukocytes. *C*. Hyaline cast with attached epithelium, truly an epithelial cast.—(*Landois.*)

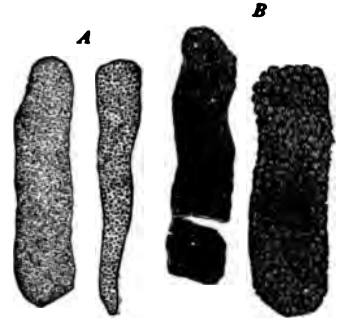

FIG. 92. — GRANULAR CASTS. — (*Landois.*)

A. Granular casts in which the granules are fine and the dissolution of the epithelial cells is complete. *B*. Granular casts in which the granules are coarse and the outlines of the epithelial cells at points faintly distinguishable.

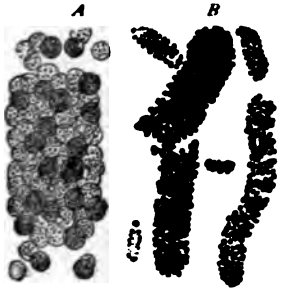

FIG. 93.

A. Cast made up almost purely of leukocytes. *B*. Casts composed of acid sodic urate; crystalline casts.—(*Landois.*)

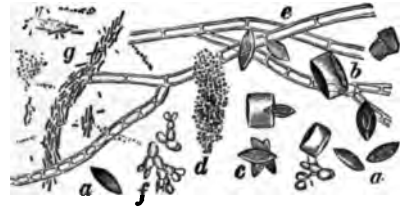

FIG. 94.

a, *a*, *b*, *c*. Crystals of uric acid. *d*, *g*. Zooglea masses of cocci and bacilli. *e*. Mold. *f*. Yeast.—(*Landois.*)

FIG. 95.—SOME FORMS OF URIC ACID.

1. Rhombic crystals. 2. Whetstone forms. 3, 3. Quadrate forms. 4, 4, 5. Irregular forms. 6, 8. Groupings into roset forms. 7, 9. Bundle forms, precipitated by adding hydrochloric acid to the urine. The crystals may be pigmented or lightly colored brownish-yellow; the pigment is presumed to be uroerythrin, also called urochrome.—(*Landois.*)

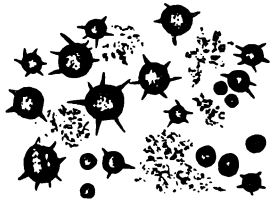

FIG. 96.—ACID AMMONIUM URATE.

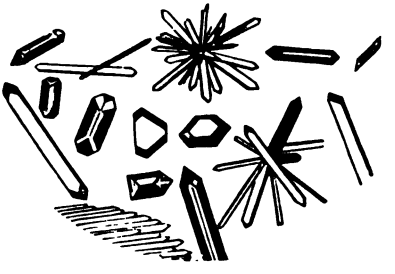

FIG. 97.—HIPPURIC ACID. FOUR-SIDED PRISMS WITH TWO OR FOUR BEVELED EDGES.—(*Gould.*)

FIG. 98.—SOME DEPOSITS IN ACID FERMENTATION OF THE URINE.—(*Landois.*)
a. Bacteria. *b.* Amorphous sodic urate. *c.* Uric acid. *d.* Calcium oxalate.

FIG. 99.—SOME DEPOSITS FROM AMMONIACAL URINE (ALKALINE FERMENTATION).
a. Acid ammonium urate. *b.* Ammoniomagnesium phosphate. *c.* Bacteria.

FIG. 100.—WHETSTONE AND IRREGULAR CRYSTALS OF URIC ACID.—(*Gould.*)

FIG. 101.—AMMONIUM URATE. "HEDGE HOG" CRYSTALS.—(*Gould.*)

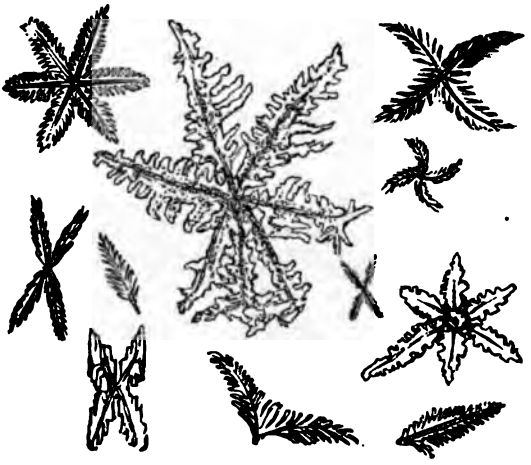

FIG. 102.—STELLATE AND FEATHERY CRYSTALS OF TRIPLE PHOSPHATE.—(*Tyson.*)

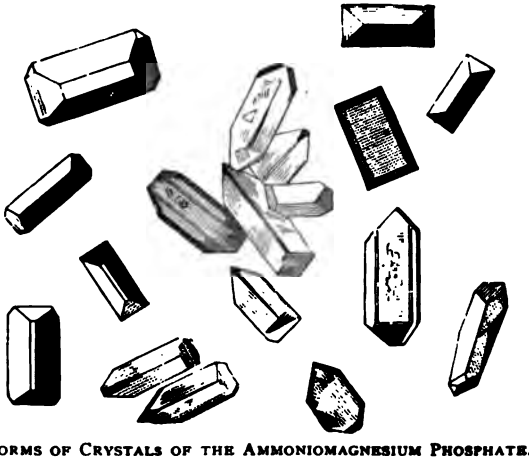

FIG. 103.—FORMS OF CRYSTALS OF THE AMMONIOMAGNESIUM PHOSPHATE.—(*Tyson.*)

FIG. 104. — AMMONIOMAGNESIUM PHOSPHATE (TRIPLE PHOSPHATE).—(*Gould.*)

Triangular prisms with beveled edges; "coffin-lid" crystals.

FIG. 105.—MAGNESIUM PHOSPHATE.—(*Gould.*)

Elongated rhombic tablets, which may be fused together in variously formed masses.

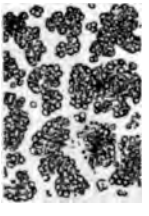

FIG. 106.—AMORPHOUS GRANULES OF CALCIUM CARBONATE.—(*Gould.*)

FIG. 107.—OXALATE OF LIME.

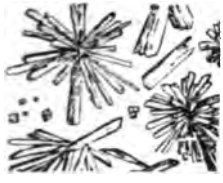

FIG. 108.—AMORPHOUS GRANULES, WEDGE-SHAPED CRYSTALS, SOME ARRANGED IN ROSETS OF CALCIUM PHOSPHATE.—(*Gould.*)

FIG. 109.—DUMB-BELL AND OCTAHEDRAL CRYSTALS OF CALCIUM OXALATE.—(*Gould.*)

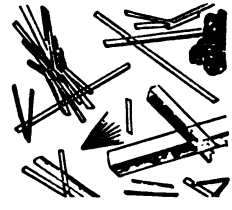

FIG. 110.—CALCIUM SULPHATE; ELONGATED TRANSPARENT NEEDLES OR TABLETS.—(*Gould.*)

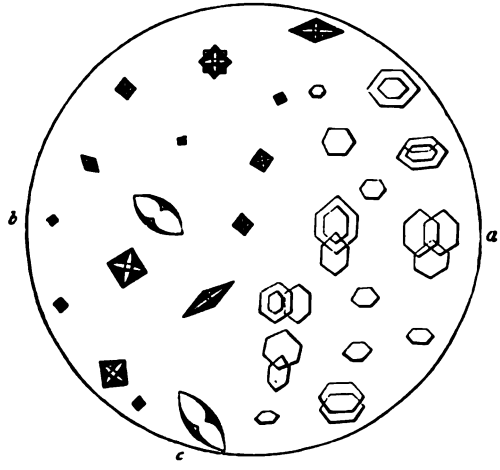

FIG. 111.

a. Crystals of cystin. *b*. Crystals of oxalate of lime. *c*. Hour-glass forms of *b*.

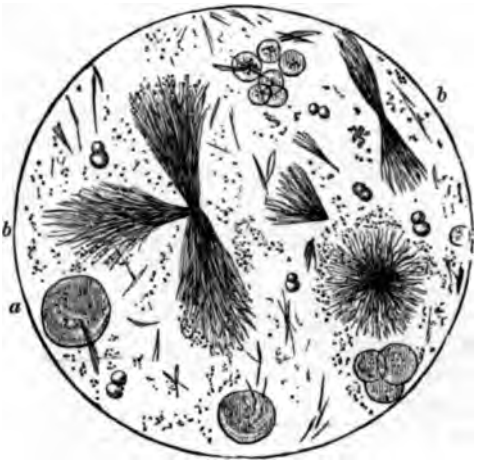

FIG. 112.
a. Leucin balls. *b*, *b*. Tyrosin sheaves.

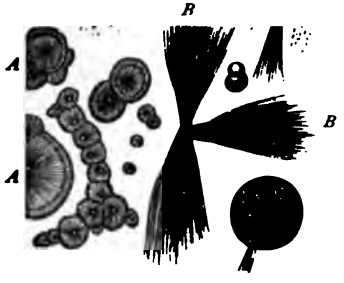

FIG. 113.—LEUCIN AND TYROSIN.
A, *A*. Leucin; yellowish, highly refracting spheres, with radiating lines. *B*, *B*. Tyrosin, needles and sheaf.

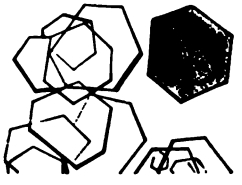

FIG. 114.—CYSTIN, SIX-SIDED PLATES, OFTEN SUPERIMPOSED.—(*Gould.*)

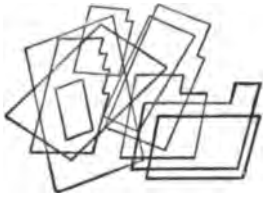

FIG. 115.—CHOLESTERIN.—(*Landois.*)

FIG. 116.—INDIGO.—(*Gould.*)
Amorphous granules, fine needles, and crystals of a blue color.

CHAPTER V.

TECHNIC OF SPUTUM EXAMINATION.

Collecting the Specimen.—Great care should be exercised in obtaining the sputum for examination. Avoid the collection of sputum immediately after eating, as, under such circumstances, it contains particles of the food, which unnecessarily complicate the examination. The first sputum raised in the morning is to be preferred. An effort should be made to instruct the patient to avoid collecting mucus brought from the nose and pharynx. The amount of sputum to be obtained will, of course, vary with circumstances: while a very small amount may be examined and give satisfactory results, five or ten cubic centimeters or more should be obtained when possible. Have the patient expectorate directly into a small stone cup or sterilized salt-mouth bottle; as soon as a sufficient quantity of sputum has been collected, the container should be at once sealed with adhesive plaster or tightly corked, and labeled. When ready for examination, the sputum should be poured upon a piece of ordinary window glass with the under side painted black, or a Petri dish placed over a blackened surface. Upon this black surface the small, white, opaque portions, which are best for examination, can be readily seen, removed by forceps or platinum hook, and placed in the center of a glass slide. A cover-glass is laid on the specimen, and slight pressure made to obtain a uniform layer.

FIG. 117.—SQUAMOUS EPITHELIUM.
Often found in sputum and in urine. In the former it is from the mouth or pharynx. In urine it is usually from the vagina.

White blood-corpuscles are found in all sputum.

Red Blood-corpuscles.—Their presence in small numbers is not significant. In pneumonia they occur as pale, discoid bodies, and in hemoptysis the sputum may consist almost entirely of red corpuscles.

Epithelium.—Squamous, from the mouth.

Ciliated, usually from the trachea and bronchi.

Alveolar, from the alveoli of the lungs.

Elastic Fibers.—When these fibers display an alveolar arrange-

ment, they have been derived from the pulmonary alveoli, and indicate a destruction of lung tissue.

They occur in tuberculosis and bronchiectasis, and occasionally in pulmonary abscess and pneumonia. The slide of sputum is prepared in the usual way, and examined with a $\frac{1}{6}$-inch objective.

The elastic fibers exhibit a double contour, are dark colored,

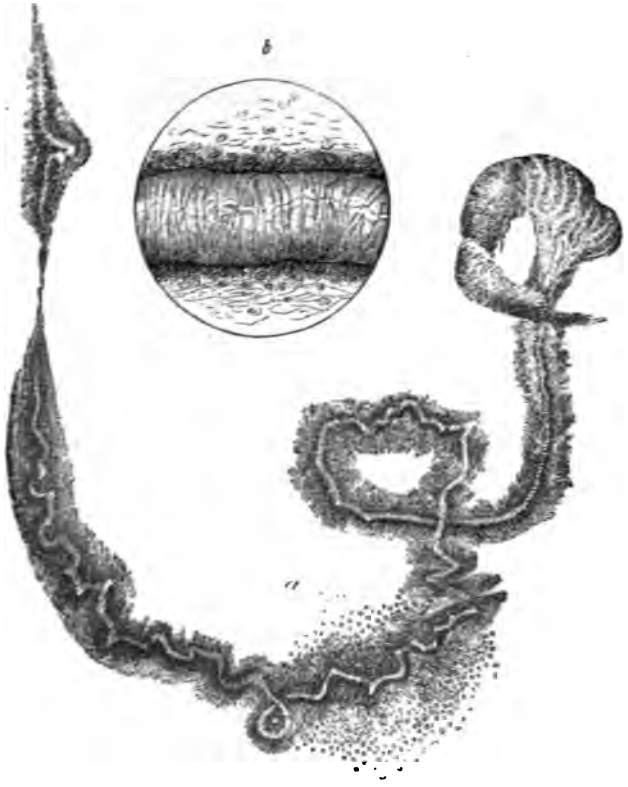

FIG. 118.—CURSCHMANN'S SPIRALS.—(*Schmaus.*)
a. × 80 diameters. *b.* × 300 diameters.

slightly curved, and vary much in length and breadth. They can be most readily collected for demonstration by rapid sedimentation in a centrifuge.

Curschmann's spirals are found in sputum of asthmatic patients, and appear as thick white bodies having a twisted tubular form. When examined with a low power, they show a central,

highly refracting, twisting thread, around which is a meshwork of delicate fibers. They require no stain.

Fibrinous casts are tree-like casts of the terminal bronchial tubes, found in bronchitis and pneumonia, and composed of fibrin or mucin containing entangled cellular elements. (See Fibrinous Inflammations of Mucous Membranes.)

Charcot-Leyden Crystals.—These crystals are colorless, have a

FIG. 119.—CHARCOT-LEYDEN CRYSTALS.—(*Landois.*)

pointed octahedral form, and are found chiefly in the semi-solid, grayish-yellow pellets discharged during an asthmatic attack.

Tubercle Bacillus.—(For technic of examination see article on Bacteriology.)

Bacillus of leprosy occasionally occurs in sputum. (For technic of examination see article on Bacteriology.)

Pneumobacillus, Pneumococcus (Friedländer, Fränkel).—(For technic of demonstration see article on Bacteriology.)

PART II.

GENERAL PATHOLOGY.

PART II.—GENERAL PATHOLOGY.

CHAPTER I.

General pathology comprehends those variations in structure and function that may attack any organ. It is the study of morbid processes independent of their location, while **special pathology** is the study of diseases of organs independent of the same disease occurring elsewhere than in the organ under consideration.

By **development,** pathologically, we mean the growth of tissues into organs—the proliferation or production by arrangement or otherwise of a tissue not identical with that from which the original cells arose; thus, in the development of the fetus, certain cells give rise to different organs—the alimentary canal, including the pancreas and the liver, arises from cellular elements that are identical. These organs are not produced by mere growth, but are dependent upon the process of development.

Growth is the increase in size of an organ by proliferation of its normal cellular units; theoretically, with a single liver lobule a whole liver could be produced by the mere process of growth.

Our knowledge of the **normal** is obtained by studying healthy individuals or organs not manifesting disease, and considering as normal that condition which is commonest. Any deviation from the normal must come under one of three heads —*malposition*, *malformation*, or *disease*.

1. **Malposition** is the misplacement of an organ from that position in which it is most commonly found, or any alteration of its relation to other organs. The heart may be rotated on its axis and not occupy the normal relation to the surrounding tissue, and still the heart may be in place; so that malposition implies either that the organ is not in place, or that, being in place, its parts do not bear their normal relation to surrounding structures themselves normally placed.

Malpositions may be **congenital** or they may be **acquired.** Congenital forms are by no means always permanent, although they usually are. The acquired forms are less likely to be so, although, if they persist, such changes may occur as to render them incapable of resuming normal positions and relations. Hernia may be congenital or acquired, and in either case may become permanent through adhesions, inflammation, etc. The heart may be pushed to the right side by a left-sided hydrothorax, and return to its normal position with the subsidence of its causative lesion. If the heart be transposed with other viscera during intra-uterine life, the position assumed becomes permanent, although the organ may be in nowise diseased.

2. **Malformation** is a deviation in structure or in development from that which is most commonly found. A malformed organ may not be a diseased organ, so that malformation, like malposition, is not of necessity disease; as to whether it was brought about by previous disease or not is a question that can not always be determined; so that a malformation may be the result of maldevelopment,—*congenital malformation*,—or it may be acquired as the result of disease; in the same way acquired malpositions may occur. *Acquired malformation* is commonly called *deformity: e. g.*, the deformity following fractures, accompanying dislocations, or due to tumors or swelling.

3. Morbid processes induce or are expressions of **disease,** and this disease may be manifested as a **disease of structure** (**organic disease**) or **disease of function** (**functional disease**). It is probable that there is always a lesion of structure in order to produce a lesion of function, and that the so-called functional diseases, such as palpitation of the heart, are due to changes in the innervation, temporary in character, and brought about by stimulation or depression by chemic elements circulating in the blood or arising in organs, such elements not being a part of the normal chemistry. Disease of structure usually means disease of function; but the fact that tissue is supplied in excess of the common demands of organic life leaves room for considerable loss of structure or modification of tissue without apparent alteration in function. If reduced to its last analysis, we may define disease as any tissue alteration or structural change that alters the function of the integral elements of which a tissue or organ is composed, such alteration of function being beyond the limits of that which is normal.

Pathogenesis or Cause of Disease.—Whatever may be the change going on in an organ or tissue, we must believe that it

has a cause, and that the manifestation which we recognize as disease represents the reaction of the normal to some influence: some entity, the exact character of which may not be known. Like all other manifestations of force (whether it be light, or heat, or the activity of cells depending upon those cell changes that we recognize as nutrition—conversion of force or energy by chemic changes), they all must have some starting power, some cause. This cause so enters into the process that it is a most important part, and therefore the study of disease implies a knowledge of its cause. The acting cause induces a certain perversion from the normal, which constitutes the morbid process, and this marks its pathway by results. Investigation of disease implies a study of the **cause,** the **effect** (the cause acting), and of **result,** or the effect terminated. So far as its influence on life is concerned, the result may be more disastrous than the active process. As an example of this fact, we observe a gumma of the larynx, in which the most obstinate symptoms manifest themselves after the absorption and cicatrization of the lesion begins, and the stenosis of contracting fibrous tissue threatens life by occlusion of the air-passage.

CAUSES OF DISEASE.

The continuance of the chain of phenomena the manifestations of which are relatively constant in health is dependent upon causes some of which are well known, while of others we know little or nothing. Changes in, or perversions of, activity constitute variations entering into the formation of the complete picture of disease. The alterations, structural and functional, may be dependent upon causes easily recognized; indeed, at times they may form the most conspicuous elements in the complete picture, while in other instances their subtleness may preclude accurate demonstration. All sorts of efforts have been made to classify satisfactorily these causes. For the most part such efforts have been only partly successful. The varied origins of these causes, and the many conditions under which they act, render accurate subdivision quite impossible. It has been said that many of the causes act entirely from without; these are said to be **external causes.** As an example of such a cause, trauma or injury may be cited. On the other hand, certain causes are said to rise purely within the organism—**internal causes.** Heredity is an acceptable example of this group. Again, causes are said to be **predisposing** or **exciting.** The predisposition and the exciting

element may arise either within or without the organism, and may, for this reason, belong to either of the subdivisions previously given. Predisposition may depend upon heredity, previous attacks of disease, habits, occupation, and a multitude of conditions either directly or indirectly applied. Closely associated with predisposition to disease is a transmitted or acquired resistance to certain causative agents—a phenomenon spoken of as immunity, which will be considered elsewhere.

Starvation and Allied Conditions.—The inability of the body to secure the materials requisite for the maintenance of function, including growth and replacement of waste, is followed, more or less rapidly, by well-marked disturbances. This cutting-off of the elements requisite for nutrition may be dependent upon external conditions, or may, to a certain extent, arise from perversion of normal processes. Thus, the cutting-off of oxygen may be dependent upon its absence or scantiness in the surrounding medium, as when the body is submerged in water, or it may be due to occlusion, to spasm, or to the presence of a foreign body in the air-passages ; or, as a result of altered absorbing power, the blood may not be able to take up the gas even when the latter is abundantly supplied in the vesicular structure of the lungs. In carbon monoxid poisoning the gas seems to combine so firmly with the oxygen-carrying bodies that it can not be displaced, and no matter how rich in oxygen the inspired air may be, it is not absorbed as in health. The changes induced are largely dependent upon the extent to which the supply is diminished, the duration of the oxygen starvation, and the facilities afforded for the excretion of materials the accumulation of which is favored by the absence of the normal respiratory interchange. If the amount of oxygen supplied be but moderately diminished, the most frequent changes occurring in the fluids and organs of the body are degenerative processes, so slowly brought about as to be inconspicuous until in an advanced stage. The more marked or more rapid lessening of the supply of oxygen, such as results from pressure of exudates of tumors without the larynx or swelling within, gives rise to the condition known as asphyxia. In the production of the phenomena grouped under this heading the accumulation of carbon dioxid has probably more to do than, or certainly equally as much as, the associated diminution in the quantity of oxygen present.

Food and drink, as well as oxygen, are necessary for the maintenance of life, and a marked reduction in the supply of any of these will be associated with evident changes in the nutrition of

the organism. As is the case with oxygen, so we find with food: the intensity of the lesions produced depends largely upon the extent and rapidity with which the food-supply is reduced. Insufficient nourishment usually gives rise to lessened resistance on the part of the individual, rendering him more susceptible to the action of causes that, under ordinary circumstances, would produce no effect. With the complete withdrawal of food and water there is rapid combustion of the fats of the body, associated with the destruction of the proteids and the rapid loss of water. The tissues whose functions can be best spared suffer most. This fact is supported by the early utilization of the fat, by the progressive wasting of the skeletal muscles, and by the fact that the heart, kidneys, and nervous system are the last to suffer and are the least altered. Parenchymatous changes are observable in nearly all the organs, and toward the last these changes may become marked in organs the function of which is absolutely necessary for the maintenance of life. In addition to the absence of food and the fact that the body must, in a certain way, consume its own tissue to maintain heat and to supply the force requisite for carrying on respiration, circulation, etc., there is also an accumulation within the body of poisons that tend to induce the disintegration of tissue elements.

Ordinarily, the occurrence of starvation is dependent upon the inability of the organism to obtain food; but occasional instances occur in which, as a result of degenerative lesions of the mucosa of the alimentary canal, and from other causes, the power of the organism to digest or to assimilate available pabulum is lost, and death occurs as a result of starvation, although abundant food is supplied. Starvation may result from more or less marked occlusion of the esophagus by stricture, tumors, etc.; under such conditions, before the advent of modern surgery, cases of starvation were occasionally observed. As before indicated, starvation may be dependent upon lesions of the secondary as well as of the primary assimilative forces. Thus, in certain blood dyscrasias the error of assimilation seems to be not in the digestive organs, properly so called, but in the power of the system to utilize the material supplied.

Food supplied to the body or to an organ is utilized for replacing waste, for maintaining growth, when this is necessary, and for the continuance of other functions. If an organ be called upon to accomplish more work than is possible with the food available, it is overworked, and the results of this overwork become at once manifest. These are not unlike the alterations dependent upon the cutting-off of food; in fact, the two

conditions are essentially similar. An organ doing little or no work utilizes but little pabulum; on the other hand, a greatly overworked organ may demand more nutrition than may be available, or the very fact that it is manifesting excessive functional activity may lessen its power to assimilate the nourishment supplied. In addition to the foregoing, nourishment of an organ is dependent not only upon its reception of the required amount of food, but also upon its ability to throw off the products of its own activity. An organ greatly overworked may be so situated as to permit accumulation in its interior of one or more poisons the presence of which exerts a deleterious influence upon the cellular elements of the organ in question. As an example of this form of exhaustion, which is really but another name for starvation, may be mentioned the important structural lesions noted by Hodges in the ganglion cells of pigeons. It has been said that tissues are not nourished, they nourish themselves; for the proper execution of this function food must be supplied, the cell must be able to utilize the pabulum, and removal of effete material must be sufficient; failure in the fulfilment of any of these requirements leads to structural lesions, and thereby to disease.

The **thermal causes of disease** may be grouped under several headings: (1) The local influences of very high and of very low temperatures as applied directly to cutaneous or mucous surfaces; (2) the influence of elevated temperatures upon the heat-coordinating apparatus of the individual; (3) the influence of cold on the structure and function of tissue.

Burns and Scalds.—The local changes induced by exposing tissues to elevated temperatures are dependent upon the tissue, the length of exposure, and the height of the temperature. The more delicate tissues are susceptible to slight rises of temperature, while the palm of the hand and sole of the foot may be accustomed to withstand temperatures which would be destructive to tissues richer in juices and cellular elements. Comparatively low temperatures—120° to 140° C.—may be followed by vesication and necrosis; in individuals whose resistance is depressed by hemorrhage, exhausting sickness, or similar conditions, even lower temperatures may be destructive to vitality. When the temperature is comparatively low,—115° to 130° C.,—the length of time of the exposure determines, to a large degree, the extent of the injury. Ordinarily, the local application of temperatures under from 120° to 122° C. is not associated with any marked structural change. When, however, temperatures begin to ascend above this point, cell destruction is likely

to occur, associated with the formation of exudates of various kinds and with inflammatory processes of varying degrees of intensity.

With regard to the local application of cold, the changes brought about, when the reduction of temperature is sufficient, very closely resemble those produced by high temperatures. The application of liquefied air produces such extensive necrosis that it has been proposed to utilize the agent as an escharotic, exactly as caustics may be applied, for the destruction of morbid growths.

Attempts have been made to classify burns according to their intensity or to the extent of the destruction induced; such classifications must, of necessity, be arbitrary, as all degrees and stages must merge into one another, there being no sharp lines of demarcation. Thus, it is said, we may have *burns of the first degree* associated with slight hyperemia and followed by a more or less superficial desquamation. *Burns of the second degree* give rise the the formation of blebs, with liquefaction necrosis and exfoliation of a certain amount of destroyed tissue, but not involving all the layers of the skin. *Burns of the third degree* involve the entire skin, and terminate in the formation of eschars composed largely of that structure; while *burns of the fourth degree* imply a still more extensive destruction of the tissues, amounting practically to carbonization.

These classifications are largely concerned with the local influences of the heat, and do not take into consideration the systemic phenomena. The latter are dependent more upon the amount of surface involved than upon the degree of the burn. When over one-third of the cutaneous surface is seriously inpaired by the burn, the injury is likely to prove fatal. A number of theories have been advanced to explain this well-known fact. When death follows immediately upon the inception of injury, probably the only factor with which we have to deal is shock. When, however, death occurs some time later,—preceded by focal hemorrhages and necroses in one or more organs, particularly in the alimentary canal and liver, and by hematuria, hemoglobinuria, and other evidences of violent intoxication,—it must be evident that we are dealing with something more than shock pure and simple. Among the explanations which have been offered the following may be mentioned:

(1) Suppression of the cutaneous functions of the area involved; (2) perturbed or altered nervous system, the perturbation or alteration being dependent upon reflex phenomena; (3) the formation of toxic substances in the blood; (4) the destruc-

tion of blood elements; (5) the absorption of ptomains or other poisons from the injured area. As experimental evidence can be adduced to show that poisons are present in the blood under such circumstances, it may be reasonable to presume that they are influential in bringing about the fatal terminations. Exactly what is their origin or their character must remain for the present an open question.

As a result of exposure to considerable elevation in the temperature of the surrounding medium, the heat-coordinating power of the body may be altered in a quite characteristic manner, giving rise to the well-recognized condition known as **sunstroke**—a morbid process dealt with elsewhere.

With regard to the *influence of cold*, as previously stated, the local application of extremely low temperatures induces changes closely resembling those produced by heat. An extremely low temperature in the surrounding medium, aside from the local changes, brings about a more or less gradual reduction in the activity of the body functions, and eventually causes death. Exposure to very low temperatures is slowly followed by reduction of the temperature of the body. When this reduction exceeds about 13° C., it is likely to prove fatal. When the temperature of the body is reduced to 26° C., or possibly a degree or so lower, recovery is possible; after apparent recovery the temperature may rise above the normal, and death, preceded by more or less fever and emaciation, sometimes occurs even at this late period.

Trauma as a cause of disease can be little more than mentioned at this point. Its relation to morbid processes will become more evident as we proceed. As a result of trauma, more or less destruction of tissue occurs, associated with laceration and fragmentation of adjacent or more resistant cells, which, though not actually destroyed by the injury, are no longer capable of resuming active functions, and eventually break down. During the absorption and removal of the dead tissue certain poisons are formed the activity of which, in the production of both local and systemic symptoms and lesions, can not be overlooked. Aside from these direct results of wounds, whether the latter be large or small, we have the possible introduction of irritants, which may further injure the tissue. The irritants introduced by wounds may be microscopic, and of themselves of but little importance: for example, the pigment introduced in tattooing. As a result of the acicular character of certain introduced bodies, such as scales of steel, more extensive cellular alteration may be brought about. Again, these bodies may be poisons, giving rise

to extensive degeneration, necrosis, and inflammation, such as is seen in and around the matrices of the nails, or in the skin as a result of injury and the introduction of the cyanid salts used in photography. Aside from the direct destructive influence of injuries and the incidental introduction of inorganic bodies, irritant and otherwise, the introduction of infective bodies—bacteria of all kinds—may be mentioned at this point, although they will be more specifically considered in connection with bacteria, and again with the consideration of wounds, repair, etc. The possible relation of tumor formation to trauma will be considered elsewhere. (See Tumors.)

Alterations in Atmospheric Pressure.—A sudden fall of atmospheric pressure, such as is observed in balloon ascensions and in mountain climbing, may give rise to palpitation of the heart, respiratory embarrassment, mucous and submucous hemorrhage, unconsciousness, and even death. More or less prolonged residence in a rarefied atmosphere may be associated with an increase in the number of red blood-cells in the peripheral circulation and an increase in the amount of hemoglobin. Many of the symptoms have been attributed to lack of oxygen or to the inability of the blood to absorb oxygen in its more rarefied form, and also to the influence of rapid evaporation of water that takes place under lessened atmospheric pressure.

Laborers in caissons and divers suffer, on their return to the normal atmospheric pressure, from a series of phenomena to which has been given the name *caisson disease*. So far as can be determined, the structural changes induced, and certainly the symptoms, do not manifest themselves until after the return from the caisson to a considerably lower atmospheric pressure. The symptoms observed in this condition are not unlike those seen from lowering of the normal atmospheric pressure to which the individual is accustomed; the most marked difference being in the presence of capillary hemorrhages in the central nervous system, and particularly in the meninges of the cord, associated with certain degenerative lesions in the cord itself.

Electric discharges as causes of disease have assumed considerable importance since the wide-spread introduction of electricity. The burns produced by electricity manifest nothing peculiar or characteristic, with the possible exception of vagaries in distribution. As a rule, the phenomena induced by electric discharges are most marked in intensity at the time of their occurrence, and rapidly disappear; only in rare instances do we find that they persist. The effects of electric shock are, of course, dependent upon the intensity and duration. In *lightning-*

stroke one not uncommonly finds the clothing torn, and sometimes distributed in fragments some distance from the body. The foot covering, probably by reason of its immediate contact with the earth, and possibly as a result of changes in its conductivity and of irregularity of moisture in its interstices, commonly suffers most. The practically instantaneous death that results from discharges possessing a voltage exceeding 1000 seems to arise from an almost immediate arrest of respiratory and cardiac action, the latter preceding the former.

Morbid processes induced by poisons depend upon the character of the poison and upon the susceptibility of the animal. Certain poisons act directly as destructive agents, killing and structurally disorganizing the living elements with which they come in contact. As members of this group may be mentioned the *escharotics*. Other poisons give rise to changes in the viscera, upon which they may show a selective activity, while the members of another group expend their noxious power upon the blood, and others, again, upon the central nervous system.

With regard to the origin of poisons, many may be properly classified as belonging to the mineral kingdom, among which mercury, copper, iron, arsenic, silver, zinc, iodin, bromin, etc., alone or in combination, may be cited as the best examples. Among the poisons derived from the vegetable kingdom may be cited the alkaloids of opium, cinchona, belladonna, calabar bean, ergot, etc., and the poisons produced by bacteria, to which reference will be made later. The power of animals to elaborate poisons is shown in the venom of serpents, the vesicating principle in Spanish flies, and the poisonous products of certain mussels.

In addition to animal poisons largely or purely extraneous in point of origin we must not forget that the body is constantly elaborating many poisons, the accumulation of which would of necessity be fatal. As clinical examples of these autointoxications, jaundice, uremia, and copremia may be cited.

As a result of perverted activity or loss of function there may be retention and accumulation within the body of certain noxious agents, which should be further elaborated or excreted by the organism, or, as a result of failure in the secondary assimilation, we may have the excretion of bodies normally utilized by the economy. As an example of a morbid process brought about by faulty or misdirected function in a gland whose secretion may be properly classed as internal is to be cited myxedema, resulting from disease or extirpation of the thyroid gland.

The animal parasites as causes of disease will be considered further on.

BACTERIA AS CAUSES OF DISEASE.*

Bacteria are microscopic unicellular organisms. By the earlier investigators they were thought to be animal cells, belonging to the class infusoria; now they are universally recognized as of vegetable origin. Their classification has given rise to considerable controversy, some observers placing them among the algæ, others among the fungi. It is probably as well to consider them a distinct genus.

The size of these unicellular organisms may be inferred by the fact that of some of the medium-sized cocci from eight to twelve can be placed in a row across the surface of a red blood-cell. †

Structurally, bacteria consist of protoplasm, which at the periphery is condensed to form a layer resembling a cell-wall. A varying amount of fat is present, which in some organisms may exceed twenty-five per cent.: *e. g.*, tubercle bacillus. While a nucleus has not been demonstrated, it is probable that practically the whole cell is composed of nuclear matter, there being but a thin peripheral layer of perinuclear protoplasm.

Motility.—Many bacteria possess the power of locomotion. Motile cocci, bacilli, and rigid spirals are propelled by the exceedingly rapid vibratory motion of thin, lash-like processes, extending from the sides or poles of the organism, called flagella. (For the demonstration of flagella see page 100.) Certain of the flexible spirilli possess the power of moving from place to place by (1) a rotatory motion in their long axis, or (2) by an undulatory or snake-like movement.

FIG. 120. — PROPAGATION BY FISSION. — (*Coplin and Bevan.*)

Reproduction of the schizomycetes is principally by the process of *fission: i. e.*, a cell having reached its full development, simply divides into two or more segments. Reproduction also takes place by *spore formation.* Two kinds of spores have been described: (1) Arthrospores and (2) endospores.

Arthrospore formation is described by de Bary and Hueppe as occurring in cocci. In certain chain cocci there are a few cell elements that acquire those characteristics common to spores

* For bacteriologic technic see chap. III, part I, p. 73.

† The measurement of bacteria is usually made in microns. The term "micron" is an abbreviation for micromillimeter, which is the one-thousandth part of a millimeter; in other words, about the twenty-five-thousandth part of an inch. The word "micromillimeter," or "micron," is practically never written out but indicated by the Greek letter μ.

without any apparent differentiation of cell protoplasm. They appear larger than the other elements of the chain; their borders are more sharply defined, and the cell-wall appears to be thicker; they possess a much greater resistance than the other cells to all conditions incompatible with life, and their protoplasm is darker or more highly refractile. When these bodies are removed from conditions that brought about the death of the other chain elements, and when they are placed in favorable soil, they will develop the characteristic chains.

If the nutrient media upon which the bacterium zopfii is being cultivated becomes exhausted, the organisms are, by a process of fission, resolved into a number of more or less spheric bodies possessing the properties of spores.

Endospore formation is the development in an organism of spheric or oval bodies possessing unusual resistance to conditions incompatible with the life of the mature organism. Usually the spores make their appearance only when germ plasma manifests degenerative changes and becomes granular. The spore appears at first as a small, bright point, which gradually increases in size until its diameter may exceed that of the parent cell. Frequently the spore develops in the center of the organism, when, if the organism is a bacillus, it may appear spindle-shaped. If the spore develops at one of the poles of a bacillus, the organism will appear club-shaped or pendulum-like—a characteristic of the bacillus tetani. The spores, however, may develop at short intervals through the entire extent of the bacillus, when the organism will present a bead-like or chain-like appearance, as seen in anthrax. Under favorable conditions, spores always develop into organisms identical with those from which they were derived.

FIG. 121.—FROM CULTURE OF BACILLUS MEGATERIUM.

Showing development of spores within the capsule or bacillary envelop, which, later, breaks up and liberates the spores. On the extreme right are shown three bacilli developing from the spores. —(*Coplin and Bevan.*) × 800 diameters.

Endospore formation occurs principally in bacilli, but also in spirilli. Zopf has described the formation of endospores in certain micrococci, and Escherich in the sarcina pulmonum.

The processes of reproduction, as seen in yeasts and molds, are described and illustrated with those fungi.

We can not distinguish between the many species of any one kind of organism by morphologic peculiarities alone, therefore we must develop biologic characteristics to serve us as a guide to their recognition. Thus, for instance, we know that there exist several varieties of the micrococcus pyogenes that morphologic-

ally are identical, and, were it not for certain biologic peculiarities, we could not tell one from the other. Those points commonly worked out will be found tabulated in the chapter on Bacteriologic Technic. (See p. 116.)

Microorganisms forming pigment in the process of growth and development are known as **chromogenic bacteria,** or **chromogens.**

Zymogenes, or **zymogenic bacteria,** are those capable of inducing fermentation.

Pathogenic bacteria are the disease-producing organisms.

Pathogenesis.—Koch has formulated, as conclusive evidence of the specificity of a given organism, the following requirements, which must be met:

1. *The organism must be present in all cases of the disease.*
2. *It must be cultivated in pure culture.*
3. *It must produce the disease by inoculation in susceptible animals.*
4. *From such animals the germ must be obtained and again cultivated in pure culture.*

To this cycle of proof has recently been added another demand for experimental evidence of pathogenicity:

5. From cultures of the organism there should be demonstrated a toxin that, without the germ, will produce the phenomena of the disease, or by means of which an antitoxin or immunizing substance can be developed in susceptible animals, lessening or removing their liability to the disease presumed to be produced by the organism in question.

Any evidence less conclusive than that afforded by the foregoing requirements may be considered as presumptive knowledge of specificity. So many diseases occur in man and not in lower animals that the best we can hope to do in such cases is to produce, by experiment or otherwise, as much of the proof as possible, and to accept the germ as the cause in the absence of any equally or any more rational conclusion. In some diseases—for example, leprosy—this is practically the stage at which the scientific inquiry at present rests.

Toxicogenic Bacteria.—Certain bacteria are endowed with the property of elaborating poisonous bodies without themselves being able to exist in the living tissues. As will be pointed out later, all disease-producing bacteria are toxicogenic to a certain degree.

Liquefaction.—Those bacteria that in their growth liquefy Koch's flesh-peptone-gelatin are known as liquefying. They probably elaborate a ferment having this property. The exact

ferment to which this liquefaction is due is a member of the proteolytic enzymes. Organisms not having this property are known as the nonliquefying bacteria.

The power of **producing gas** is marked in some forms of bacteria and is absent in others. (See p. 98.)

Some bacteria **coagulate milk**, and this may be used as a test in studying species. (See p. 74.)

Reaction.—During the growth of many organisms the reaction of the medium may be changed, showing the production of an acid or an alkali or a splitting-up of the body upon which the reaction of the culture medium depends. (For method of demonstrating this change see p. 101.)

Stain Reaction.—Many bacteria possess more or less constant stain reactions, and a few microorganisms are identified, in part at least, by their taking certain dyes or staining by certain methods. The special methods are given with each organism, but the following list of bacteria, with their reactions to Gram's method, is introduced for convenience of reference :*

Stained by Gram's Method.	*Not Stained by Gram's Method.*
Bacillus of diphtheria.	Bacillus pyocyaneus.
Pseudodiphtheria bacillus.	Bacillus typhosus.
Bacillus of anthrax.	Bacillus coli.
Bacillus of tetanus.	Bacillus of symptomatic anthrax.
Bacillus of leprosy.	Bacillus of glanders.
Bacillus aerogenes capsulatus.	Proteus vulgaris.
Diplobacillus of Morax and Axenfeld.	Bacillus of influenza.
Actinomyces.	Diplococcus intracellularis.
Pneumococcus.	Pneumobacillus (Friedländer).
Staphylococcus pyogenes aureus.	Gonococcus.
Staphylococcus pyogenes albus.	Spirillum of Asiatic cholera.
Staphylococcus pyogenes citreus.	Bacillus of malignant edema.
Micrococcus tetragenus.	Plague bacillus.
	Bacillus icteroides.

Thermal Death-point.—Each organism has what is known as its optimum temperature, at which the growth is most luxuriant and above or below which it becomes less and less free as the change progresses. Eventually, temperatures are reached so high or so low that growth is arrested. Cold does not kill, but a sufficiently high temperature destroys any germ. The exact point proving destructive to viability is known as the *thermal death-point.* As moist heat and dry heat are not equally efficacious, each will have its own thermal death-point. Cultures in different media and of different ages often show marked differences in the temperature necessary to kill. (For method of demonstration see Thermic Disinfection, p. 103.)

* For technic of Gram's method see p. 96.

Aerobic and **anaerobic** are terms introduced by Pasteur to denote that an organism requires the presence or absence of oxygen as an essential to its growth. It was proposed at one time to classify bacteria upon this basis, dividing them into two groups,—aerobic and anaerobic,—but it was soon discovered that certain organisms might be cultivated either in the presence or absence of air, though such bacteria usually showed a preference for one or the other condition. This led to the introduction of the terms facultative and obligate. An *obligate organism* requires absolutely one or the other condition. A *facultative organism*, while showing a marked preference for one condition, may develop under the other. Although the hope of thus classifying bacteria has been abandoned, the terms are retained, and are now used for the purpose of description as well as aids to identification. (For technic of demonstration see p. 98.)

Photogenesis.—Many bacteria are endowed with the power of producing phosphorescence.

The faculties of producing color, fermentation, disease, etc., are simply properties, and one or all may be possessed by a single organism. Furthermore, an organism, under varying conditions, may be chromogenic or nonchromogenic, zymogenic or nonzymogenic, aerobic or anaerobic, pathogenic or nonpathogenic. Again, an organism that is pathogenic for one animal may be wholly destitute of this property when injected into an animal of another species.

Other Bacterial Products.—In the process of proliferation and growth bacteria abstract from the surrounding media certain bodies that enter into the chemistry of the cell. After subserving a useful purpose in the economy of the cell and undergoing important changes, many of these bodies are liberated. Not only are certain bodies elaborated within the cell, but, as a result of abstracting certain elements from the surrounding medium, the chemistry of the medium is changed. If the elements taken up by the germ and utilized as food are thrown off by the cell, and again enter the surrounding medium, they no longer possess the same chemic affinities, and hence do not form again the same chemic combinations. As these products are to a certain extent dependent upon the character of the surrounding medium, it can be understood that the growth of a given germ upon different media may to some degree modify its product. Different bacteria growing upon the same medium elaborate products dissimilar, chemically and physiologically; apparently, each organism produces one or more bodies as characteristic of its growth as the alkaloids of certain vegetable forms of a

higher type. Of the ultimate chemistry of many bacterial products little is known; we deal more with the results of their activity than with the bodies themselves.

Among the important products of bacterial life are soluble ferments, or **enzymes.** These are thrown off from the cell, and, entering the surrounding medium, induce chemic changes, which are probably directed toward a kind of predigestion, which enables the growing germ to obtain nourishment that previously was not in an assimilable form. Certain of these ferments split up starch in a manner resembling diastase, and hence they are called *diastatic* or *amylolytic ferments*, resembling the ferments normally present in the saliva and pancreatic juices.

Other enzymes break up the proteids, converting albumin into albumose and into peptone, and hence they are called *peptonizing* or *proteolytic ferments*. Others break up fat, and some possess the property of converting cane-sugar into glucose by a process of inversion, while other ferments lead to precipitation of the casein in milk, which may again undergo resolution in the presence of other members of the group. Through the activity of certain of these enzymes we have the occurrence of fermentation, the oxidation of carbohydrates, etc., leading to the formation of alcohols, organic acids, etc.

Various **acids** are produced by the specific action of bacteria. Among the most important are *lactic*, *acetic*, and *butyric* acids. The *bacillus acidi lactici* produces lactic acid from milk-sugar, and is considered the usual cause of acid fermentation in milk.

FIG. 122.—BACILLUS BUTYRICUS. × 1000.

FIG. 123.—BACILLUS ACIDI LACTICI. × 800.

The mycoderma aceti (bacillus aceticus) produces acetic acid in dilute solutions of alcohol in the presence of oxygen. Butyric acid is produced by a large number of bacteria; the most important one, however, is the bacillus butyricus, an anaerobic organism.

The alkali most commonly elaborated by bacteria is ammonia, which is a final product of proteid dissolution: *e. g.*, bacterial disruption of urea, leading to the formation of ammonia and carbon dioxid.

Putrefaction of animal and vegetable bodies is brought about by a great variety of bacteria. The products of this process are numerous, and are usually divided into two classes—the volatile and the nonvolatile. The malodorous gases belonging to the former group are commonly the product of anaerobic bacteria.

Novy has very properly considered putrefaction to be a putrid fermentation, it differing from other fermentative processes in the fact that the bacteria are dealing, in the change under consideration, with proteid matter, and only to a limited degree with sugars and starches.

Ptomains are basic substances containing nitrogen, and resemble in chemic constitution such vegetable alkaloids as morphin and strychnin. Like the vegetable alkaloids, in combination with acids they form definite salts. It was at one time believed that bacteria owed their disease-producing power to the ptomains. This is now known not to be the case, as a number of intensely pathogenic bacteria—for example, the diphtheria bacillus—do not elaborate ptomains.

The most important bacterial products, so far as at present known, are the **toxins.** Toxins, as elaborated by the pathogenic bacteria, resemble to a varying extent the albuminoid poisons, abrin and ricin, and the venom of serpents. While this resemblance is possessed to a varying degree by all, each toxin is the specific product of a given microorganism. Investigators are agreed that the toxins are not basic bodies like ptomains, nor are they proteids; they may be enzymes. The toxins are commonly present within the bacterial protoplasm, although they may be also found in the surrounding culture medium.

Toxins are unstable compounds, being destroyed by comparatively low temperatures (60° to 80° C.), and, in most instances, by exposure to sunlight. They are the most active poisons known: it is estimated that $\frac{1}{2\,7\,5}$ of a grain of the pure toxin of tetanus would be fatal to an adult. They are for the most part destroyed by the digestive juices of the body, and hence are innocuous when administered by the stomach. Entering the circulation, they manifest their poisonous properties upon many of the cells of the body, each toxin apparently selecting certain cellular elements, which are said to show an unusual degree of susceptibility. It is not improbable that the poison directly combines with, or is taken up by, the cells; thus, if tetanus poison be mixed with pulpified or finely divided elements from the central nervous system, and at the same time another portion of equal toxicity be mixed with some indifferent tissue, and both solutions sedimented, in the solution containing the indifferent tissue the toxin will be uniformly distributed through the supernatant fluid, while in the remaining vessel the toxin will be found most abundant in the sediment. The ultimate fate of the toxins is not known; as just indicated, the cells of the body may, to a large degree, oxidize or in some other way convert these power-

ful poisons into harmless compounds, or they may be excreted by the emunctories.

Local Effects of Bacteria and Bacterial Products.—These are dependent upon the character of the tissue involved, the organism in question, the number of bacteria, and the presence or absence of bacterial products, as well as upon local and general immunity or susceptibility of the animal. Some bacteria brought in contact with the connective tissues induce changes that are fairly characteristic. Thus, the miliary tubercle arising as a result of local infection by the bacillus of tuberculosis is, in its intimate structure, a fairly constant body. Histologically, however, the condition may be so closely simulated by other infections that the most expert histologist may not be able to decide positively as to the tuberculous character of the lesion in question. In a general way it may be said that locally bacteria and their products induce necrosis and degenerative changes, which may or may not be followed by efforts at repair. As these changes will be considered with more detail in connection with the diseases with which they arise, it will not be necessary further to describe them at this time.

IMMUNITY.

It has long been a recognized fact that a person having suffered from an attack of certain infectious diseases is more or less refractory to subsequent infection by the specific organism of that disease.

As far back as the early years of the eighteenth century it was known in Europe that the Turks inoculated their children with smallpox matter, in the hope of bringing on a mild attack of the disease and thereby inducing an immunity. To Lady Mary Wortley Montague belongs the honor of first calling serious attention to this practice, in a letter addressed to her friends in England, and dated March 23, 1718. In this letter is described the inoculation of her young son with smallpox matter. Jenner's remarkable discovery of the immunity conferred by the cow-pox virus shortly followed.

Within recent years scientists interested in the study and development of bacteriology have been called upon to explain this phenomenon, and many hypotheses have been advanced. Klebs and Pasteur believed that, in the first attack, something in the system essential to the life of the organism became exhausted, and the germ died. A recurrence of the disease wholly depended upon a renewal of this substance, and in the interim the person

possessed an immunity to the disease. Chauveau, supported by many eminent bacteriologists, believed that the immunity depended upon the accumulation in the system of bacterial products that, having arrived at a certain degree of concentration, are incompatible with germ life.

Grawitz explained the induction of immunity by assuming that in infectious diseases a conflict between the cells of the body and the germs of disease ensues immediately upon the introduction of the latter into the tissues. If the cells are victorious in the combat, they ever after should possess increased power of resistance to this particular germ, and, in fact, be able to destroy it immediately upon its entrance into the tissues.

Buchner promulgated an explanation that was a slight modification of Grawitz's hypothesis. He assumed that in every infection there is an inflammatory reaction at the point where the germs localize, and that an alteration in the cells is thereby induced that subsequently enables the cells of the economy to resist and destroy that particular germ.

Metschnikoff next advanced his now celebrated theory of **phagocytosis.** He believed that the ameboid cells of the body take into their substance the bacteria, just as they would a particle of foreign matter or an article of food, and, appropriating a portion to their own use, throw off the remainder into the blood, to be carried to and excreted by the emunctories. Although many cells of the body are competent to perform the function of phagocytosis, the typical phagocytes are: (1) The microphagocyte of Metschnikoff, the neutrophile and amphophile cells of Ehrlich, or the finely granular oxyphile cell of Kanthack and Hardy; (2) the macrophagocyte of Metschnikoff, or large lymphocyte of Ehrlich, or hyaline cell of Kanthack and Hardy;* (3) endothelium, particularly the endothelial cells of the blood capillaries, and partly, although to a somewhat unknown extent, the endothelium of the lymphatics, and even large lymph-spaces, such as the serous membranes; (4) other mesoblastic cells, particularly during active proliferation or when subjected to irritation. In this last group belong the fibroblasts of embryonic and granulation tissues, and possibly similar cells produced under other circumstances.†

Fodor called attention to the bactericidal powers of fresh

* For classification and description of these leukocytes see table in chapter on Pathology of the Blood, part III, chap. I.

† For further consideration of phagocytosis the reader is referred to the article on Inflammation.

blood-serum, and believed that immunity depended upon the presence in the body-juices of materials destructive to the bacteria. Buchner and Hankin demonstrated the presence in the blood of certain bodies that they called *alexins*, and upon the activity of which immunity was believed to depend. It was shown, however, that the bactericidal properties of the various sera did not prevent the cultivation of bacteria upon them, nor, when such sera were taken from animals naturally immune and injected into animals susceptible, did it produce immunity. Metschnikoff held that the protective agencies in the sera arose from *phagolysis* (dissolution of the leukocytes) and the retention in the blood of the anti-infectious agent normally produced and found within the phagocytic cells. As a result of these observations there has gradually evolved the **cellulohumoral theory** of immunity, which best accords with the facts established by experience or elucidated by research. Of all the theories, this probably more than any other discloses our ignorance of the ultimate mechanism of immunity. This theory presumes that there are certain "*anti-bodies*" present in the cells and body-juices of an animal, no matter what form of immunity it may possess. As the name indicates, it is based upon the belief that these substances are present in the body-juices as well as in the cells, while at the same time the tendency of investigators is to believe that these substances have their origin in the cells of the body, and that the most active cell, if not the only cell, influential in their production is the phagocyte.

A number of forms of immunity are now recognized. In the first place it is to be remembered that an *absolute immunity* to infection rarely, if ever, exists. As a rule, the highest attainable immunity may be broken down, and an animal naturally possessing extraordinary resistance to some particular form of infection may be made susceptible. Thus, the chicken, which is naturally immune to anthrax, may be made susceptible by more or less prolonged immersion in cold water. In a similar way susceptibility may be increased by starvation, improper food, fatigue, shock, hemorrhage, and associated infections.

The influence of the last-named condition in breaking down a more or less natural barrier to infection is shown by the rapidity with which individuals occasionally succumb to tuberculosis of the lungs consecutive to other infectious processes in those organs. Thus, the catarrhal pneumonia incident to measles and influenza may afford a suitable nidus for the lodgment of the tubercle bacillus, and the inflammatory changes induced by the presence of foreign bodies in the lung may act as an etiologic

factor in the induction of septic pneumonia. As further illustrating the relationship between an absolute resistance and an immunity of moderate degree, we must remember that the dose of the infectious agent may determine whether the animal will resist the disease. Thus, large doses bring about fatal results, while smaller doses, even when repeated, may only strengthen the resistance of the animal. The facts adduced go to show that there is first an immunity that approaches an absolute resistance to the disease, and, second, there is a high degree of susceptibility, which may be so marked that the smallest possible dose of an infectious agent will prove fatal to the animal in question. Between these two conditions all possible intermediate forms of reaction to infection may exist. An attempt has been made to subdivide these intermediate gradations of immunity and susceptibility into an absolute immunity and a partial immunity. Such a division is not, in the present state of our knowledge, possible.

Natural immunity is the resistance to some particular form of infection transmitted from parent to offspring. This form of immunity may belong to some particular species in the animal kingdom or may even be but one race of animals. As examples of this condition may be noted the susceptibility of the field mouse and the immunity of the white mouse to glanders; the relative immunity of the negro to yellow fever and malaria and the great susceptibility of the white race.

When an animal naturally susceptible to a disease develops immunity, the condition is known as **acquired immunity**; this may be further subdivided into active and passive immunity.

Active immunity may be brought about in a number of ways. An individual having suffered from an attack of one of the infectious diseases, such as smallpox, becomes immune to subsequent attacks; the intensity and duration of this immunity will vary with different diseases and different individuals. Thus, in smallpox immunity is almost absolute, second attacks of the disease being exceedingly rare. On the other hand, with cholera, and particularly with erysipelas, the duration of the period is short and the degree of immunity never very great. In erysipelas some practitioners believe that one attack predisposes to a second, thus indicating that instead of immunity there may be increased susceptibility. Acquired immunity may also be brought about by inoculation. The inoculation may be made with attenuated microorganisms, or with such small doses of virulent organisms that the disease is not induced; by gradually increasing the dose the animal

becomes resistant to a quantity of the infectious agent that at first would have proved rapidly fatal. As examples of immunity induced by inoculation with attenuated organisms, the protection afforded to sheep by inoculation with anthrax organisms, made less virulent by cultivation at high temperatures, may be cited. Although we do not at present know what bacteria are active in cowpox, vaccinia, or smallpox, we are probably justified in believing that vaccination induces a form of immunity properly classified here.

Again, immunity may be secured by the use of bacterial products without using the living organisms themselves. The bacterial products utilized for this purpose may be filtered toxins, derived from actively growing virulent organisms, or the cultures may be sterilized at so low a temperature (55° to 65° C.) as not to destroy the toxins and the proteid constituents of the bacterial cell, and the sterile fluid may be injected subcutaneously or intraperitoneally. The use of a sterile filtrate for inducing immunity is the method at present in vogue for immunizing animals in the preparation of diphtheria antitoxin. (See p. 110.) A certain degree of immunity may be induced by feeding animals on bacterial products, or even the bacteria themselves. As to the process by which the so-called "anti-bodies" bring about protection, we are still uncertain. It has been held that the antitoxin neutralizes the toxin exactly as acids do alkalies, or that it calls into activity the protective powers of the animal—in other words, acts as a "stimulant" to the tissue cells, which, if either of these views is the true explanation, can not be at the present time affirmed.

It has been proposed to utilize the terms induced, artificial, or experimental immunity to cover immunity brought about by experiment or inoculation, and to limit the term acquired immunity to the immunity that follows an attack of disease.

Passive Immunity.—If an animal that has been rendered immune by some of the methods previously given be bled, and the blood, or the serum separated from the blood, injected into another animal not previously immunized, the second animal acquires a more or less temporary immunity, which has been designated—by reason of its temporary character—passive immunity.

The immunity of this animal is dependent upon the presence of anti-substances taken from an actively immune animal. These substances disappear with a rapidity that varies in different animals, and with immunity against different infections. The induction of this form of immunity becomes important because of our ability to utilize it in the prevention and the treatment of

the disease. Thus, if a number of children be exposed to diphtheria, we may bring about a temporary immunity in their bodies by the introduction of a sufficient quantity of immunizing serum. This renders them immune for the time being, and they escape infection from a single exposure. Again, this kind of immunity forms a basis for the treatment of the disease already developed. As it is well known that tissues are damaged by toxins of bacteria, any agent having a tendency to prevent this action becomes an efficient agent in the treatment of the disease; hence, knowing that a child is already infected by the diphtheria bacillus, we may hope to neutralize the toxins being produced by introducing into the circulation of the patient a sufficient quantity of the antitoxin removed from an animal that has been actively immunized. Upon this basis rests the present serum therapy of diphtheria and related infections.

Local Immunity.—It has been shown that if the ear of a rabbit has been inoculated with the streptococcus of erysipelas and the animal has been permitted to recover, a subsequent inoculation, made simultaneously upon both ears, will be followed by a more active inflammation in the ear that has not been previously inoculated. It is also known that granulation tissue is more resistant to the inroads of infection than the normal tissue of the part involved. Both these facts indicate the presence of a resistance more or less restricted to limited areas. Whether this resistance is due to the presence of inflammatory products or to that of some peculiar anti-body not diffused by the circulating fluids has not been determined.

SUBDIVISIONS AND FORMS OF BACTERIA.

Owing to certain peculiarities it is possible to divide bacteria into three distinct species, which, according to Nägeli's nomenclature, are known as follows:

Mucorini, or mold fungi; saccharomycetes, or yeast fungi; schizomycetes, or fission fungi.

The mucorini and saccharomycetes play but a small part in the production of disease in man.

The **mucorini, hyphomycetes,** or **mold fungi,** as they are variously called, consist of branched, septate filaments, called hyphæ. The hyphæ frequently develop lateral filaments, which form an interlacing network called the mycelium. The mycelial hyphæ produce large mother cells, known as sporangia, in which develop a number of small, spheric, highly refractive bodies called spores.

The hyphæ segment by the cylindric cells of which they are composed, increasing in length and dividing by fission. Reproduction of mold fungi is dependent largely upon the redevelopment of the spores formed in the sporangia or conidia.

Aspergillus.—Grohe, by his investigation, was the first to show that certain varieties of the aspergillus were pathogenic for rabbits. Lichtheim's investigation demonstrated that the spores of the aspergillus flavescens and aspergillus fumigatus were actively pathogenic in rabbits. Grawitz also studied the pathogenesis of these molds, and confirmed Lichtheim's experiment. He also came to the conclusion that under certain conditions the penicillium glaucum acquires pathogenic properties: *e. g.*, when cultivated upon an alkaline medium, at temperatures of from 39° to 40° C.

The organism of **actinomycosis** is variously classified by different authorities, some placing it among the schizomycetes, others among the molds. Boström and Osler believe it to be a cladothrix. For our purpose it may be classed with the mold fungi.

FIG. 124.—ACTINOMYCES (RAY FUNGUS). FROM BOVINE ACTINOMYCOSIS. — (*Coplin and Bevan.*) × 800 diameters.

Actinomyces, or **ray fungus,** is a polymorphous organism, being found in three distinct forms:

1. Small spheric or coccus-like bodies, 0.5 μ* in diameter. These bodies are supposed to be the spores.

2. Filaments, usually about 0.6 μ in breadth. The filaments sometimes appear as though formed by the juxtaposition of a number of small rod-like or spiral bodies. Many filaments do not show this seeming segmentation. The filaments frequently become closely interwoven; some may show branches or undergo dichotomous division.

3. Club-forms, usually found in greater abundance than either of the other forms. They are regarded by Boström as degenerate structures or involution forms. Other observers, however, regard them as the true and essential reproductive structures of the organism, and claim to have discovered in them developing spores. The clubs are usually pyriform bodies composed of a limiting membrane with a clear, homogeneous, highly refractile protoplasm. They may be single or branched. They are disposed in a radiate manner about a center composed of fine gran-

*See foot-note (†), p. 147.

ular matter. The center is prone to undergo calcareous infiltration.

Stains with carbolfuchsin and by Gram's method.

Aerobiosis.—Grows either with or without oxygen.

Temperature.—Optimum, 37° C. Thermal death-point at or near 75° C.

Demonstration.—In order to demonstrate the fungus in suspected material (usually pus), spread the matter on a sterile glass plate and search carefully for yellow or yellowish-white grains that closely resemble granules of iodoform. The largest of these tufts will appear about the size of a pinhead. With a needle pick out one of these grains and transfer to a microscope slide and gently cover; examined with a low power, these grains are spheroid or globular, greenish in color, and quite opaque. While still in focus, with a needle make pressure on the cover-glass, focusing slowly downward; when the granule falls to pieces, as it soon will, under a higher power ($\frac{1}{12}$-inch oil immersion), the club-shaped masses become clearly defined. Staining is not necessary, but in sections or cover-glass spreads beautiful results may be obtained by the following: (1) Carbolfuchsin, ten minutes, gently warming the solution; (2) rinse in water; (3) saturated alcoholic solution of picric acid, five to ten minutes; (4) water, five to ten minutes; (5) fifty per cent. alcohol, fifteen minutes; (6) dehydrate in absolute alcohol; (7) clear in clove oil; (8) mount in balsam (Crookshank-Plant). Sections may also be stained in carbolfuchsin, largely decolorized in fifty per cent. alcohol, washed in water, and stained in hematoxylin in the usual manner. From cultures, the fungus stains with most of the anilin dyes.

Pure cultures are obtained by plating; the grains are crushed in the nutrient gelatin, and this is spread as usual. In order to break up the grains and to diffuse them in such a way as to secure pure cultures, it is recommended that they be rubbed up with sterile sand and plated in the usual manner. In from four to seven days the colonies appear, and are then inoculated on agar or gelatin. The agar cultures are quite characteristic, the growth first appearing as a yellowish or yellowish-red dot, enlarging upon the surface of the culture medium as a scab-like mass with elevated and thickened edges, and as it becomes older gradually browning, resembling a dried-blood scab, not uncommonly becoming black or brownish-black. Sometimes the culture medium turns brown. It grows fairly well at the ordinary room-temperature, but best between 33° C. and 37° C.

Streptothrix Maduræ.—The organism of Madura disease, or mycetoma.

Place Found.—The organism was isolated from cases of mycetoma, or Madura foot, a morbid condition occurring in India and Africa; cases have also been reported in Italy and in other parts of the continent of Europe, and a few cases are on record in this country.

Form and Arrangement.—Resembles actinomyces, showing a ray-like growth of slender mycelia with very few or no club-shaped ends. The mycelia are from 1 μ to 1.5 μ thick.

Growth.—Slowly developing organism that forms a faint white growth on agar, growing more rapidly on glycerin-agar, on which medium it develops dense colonies resembling those of actinomyces except in color; they are yellowish, later of a reddish hue. Does not coagulate milk. Forms whitish colonies on potatoes and carrots; these colonies may assume a reddish hue. Does not liquefy gelatin.

Temperature.—Grows at ordinary room-temperature, but best at 37° C. The *thermal death-point* approaches 100° C.

Aerobiosis.—Obligate aerobe.

Reproduction.—Fission and spore formation. The spores are ovoid.

Stains.—Stain by the usual anilin dyes and by Gram's method.

Pathogenesis.—Most observers have not been able to reproduce the disease by inoculation. Bocarro claims to have succeeded in monkeys, rabbits, guinea-pigs, and rats.

Demonstration.—The discharge from cases of Madura foot usually contains yellowish-gray or grayish granules, which sometimes are black, like grains of gunpowder. These granules are analogous to those already described as present in actinomycosis. Cultures may be obtained by plating in the usual manner. The method already given for isolating the ray fungus may be of value.

Achorion Schönleinii, or favus organism.

Place Found.—Present in the scale-like exfoliations and scabs of favus on man, the dog, cat, mouse, etc.

Form and Arrangement.—Stellate mycelia with hyphæ of varying thicknesses and not uncommonly branched, with swollen or irregular ends, which sometimes show buds. In old cultures the mycelia form oval, spore-like bodies, which may not separate.

Growth.—Slow growing, white or grayish, or yellowish with age. It liquefies gelatin, but does not form conidia on this medium. Forms a scaly growth on potatoes. On agar forms

a corrugated, velvety coat, which may adhere tenaciously to the underlying medium. The surface is dry and white, while the layer next to the culture medium may be light yellow. Cultures commonly give off a "mousy" odor, which is considered quite characteristic.

FIG. 125.—FAVUS FROM A MOUSE.—(*Coplin and Bevan.*) ×800 diameters.
a. Germinating tube from gelatin culture. *b*. Conidia. *c*. Formation of fruit. *d*. Mycelium threads with fructification.

Temperature.—Grows best at about 30° C.

Aerobiosis.—Aerobic organism.

Reproduction by fission. Formation of the ovoid segment referred to is presumed to be concerned in reproduction. Conidia are said to form on blood-serum.

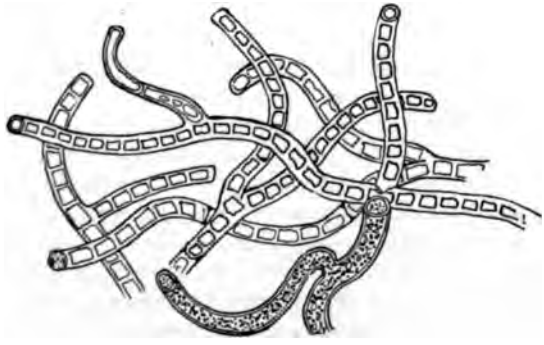

FIG. 126.—MICROSPORON FURFUR.—(*Coplin and Bevan.*) ×600 diameters.

Stain with the usual anilin dyes.

Pathogenesis.—Inoculation produces favus in the before-mentioned animals.

Demonstration.—Favus scales are macerated in thirty per cent. caustic soda or in strong acetic acid, in which they become suffi-

ciently transparent readily to show the organism without staining. By reason of the amount of corneous matter and fat present, staining of the scales is difficult. Pure cultures are best obtained by rubbing the scales up with sterile sand, as already directed for the ray fungus.

A number of favus fungi have been described, all showing certain biologic resemblance. The achorion Schönleinii (favus), trichophyton tonsurans (herpes tonsurans), microsporon furfur (tinea versicolor), are considered by Grawitz as identical with the oidium lactis.

Saccharomycetes, or Yeasts.—*Saccharomyces cerevisiæ*, the yeast used to make bread rise, is of a size most suitable for microscopic study. A small quantity of domestic yeast is shaken up with water and a drop of the mixture placed on a slide, covered with a clean cover-glass, and examined with $\frac{1}{6}$-inch or $\frac{1}{8}$-inch objective. The yeast cells are oval, round, or nearly spheroid, of varying sizes, and slightly larger than a red blood-cell. Many of them will show buds, and, if watched for a number of hours under the microscope, with the slide kept warm, the buds can be seen to form and separate, or may be seen clinging together. They may be cultivated on any of the ordinary culture media. As usually found, many cocci, bacilli, or even spiral forms are mixed with the yeast fungus, so that, when stained with the common laboratory stains, fields may be selected in which the yeast may well be compared with some of the fission fungi.

FIG. 127.—SACCHAROMYCETES CERREVISIÆ.—(*Coplin and Bevan.*) ×800 diameters.

Chromogenic Yeasts.—A number of yeasts have been isolated that, in cultures, produce color. Thus pink yeast, black yeast, red yeast, and a number of other forms have been described. In pure cultures these grow, as already described, by budding, at the same time elaborating the color peculiar to each variety.

Saccharomycetes, or *yeast fungi*, are responsible for the alcoholic fermentation in saccharine liquids. The yeast fungi multiply by gemmation, although some observers assert that the mycoderma forms ascospores. Since the appearance of Gilchrist's treatise, in 1894, numerous papers have appeared upon the pathogenicity of various yeasts.*

* "On the Pathogenic Action of Blastomycetes," Alexander G. R. Foulerton, "Journal of Pathology and Bacteriology," vol. VI, No. 1, 1899, with an elaborate bibliography, etc.

The relation of yeasts to tumor formation will be discussed later. For the present we can only say that evidence of the pathogenicity of certain yeasts is accumulating, but much remains undemonstrated and requiring further research. Many of the yeasts are capable of easy cultivation, and can be stained readily with the ordinary anilin dyes and by Gram's method. The only disease at present held to be attributable to yeast fungi is *thrush.*

Monilia Conidia (*Oidium Albicans; Saccharomyces Albicans; Thrush Fungus; Soorpilz* (German); *Muguet* (French)).—Mycelium formed of branched, septate filaments. Conidia, oval or spheric in shape, develop at the extremity of the mycelium, or a lateral septum. The branched hyphæ consist of short cylindric cells, which vary slightly in thickness. On milk, bread-paste, potato, and other culture media the oidium albicans rapidly forms a milk-white growth, extending as thread-like, almost colorless projections into the substratum. Stains with usual anilin dyes. By some authorities this organism is believed to be intermediate between the molds and yeasts.

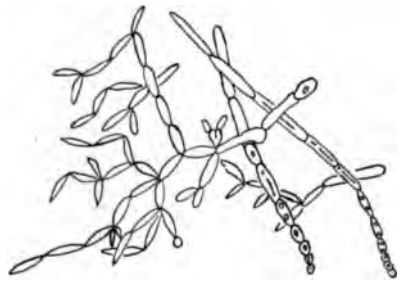

FIG. 128.—SACCHAROMYCETES ALBICANS (THRUSH FUNGUS).—(*Coplin and Bevan.*)

The **schizomycetes** form the most striking group of the bacteria, and include all the important disease-producing germs. For convenience in study, we may subdivide the schizomycetes into three varieties, according to morphologic peculiarities.

Schizomycetes: (I) Cocci; (II) bacilli; (III) spirilla.

I. *Cocci.*—Spheric, slightly ovoid, or lancet-shaped bacteria, which reproduce by binary division, and occasionally by the formation of arthrospores.

The cocci form such complex varieties that a further subdivision will be necessary to facilitate our study of them:

By number	Monococci. Diplococci. Tetracocci.	By arrangement	Streptococci. Micrococci (staphylococci). Ascococci. Sarcinæ.

Varieties.—Diplococci: cocci associated in pairs. Tetracocci: cocci associated in fours. Monococci: cocci not definitely asso-

ciated in any manner with one another. Streptococci: cocci arranged in such a manner as to form chains; the chains may contain thirty or more elements. Micrococci (staphylococci):

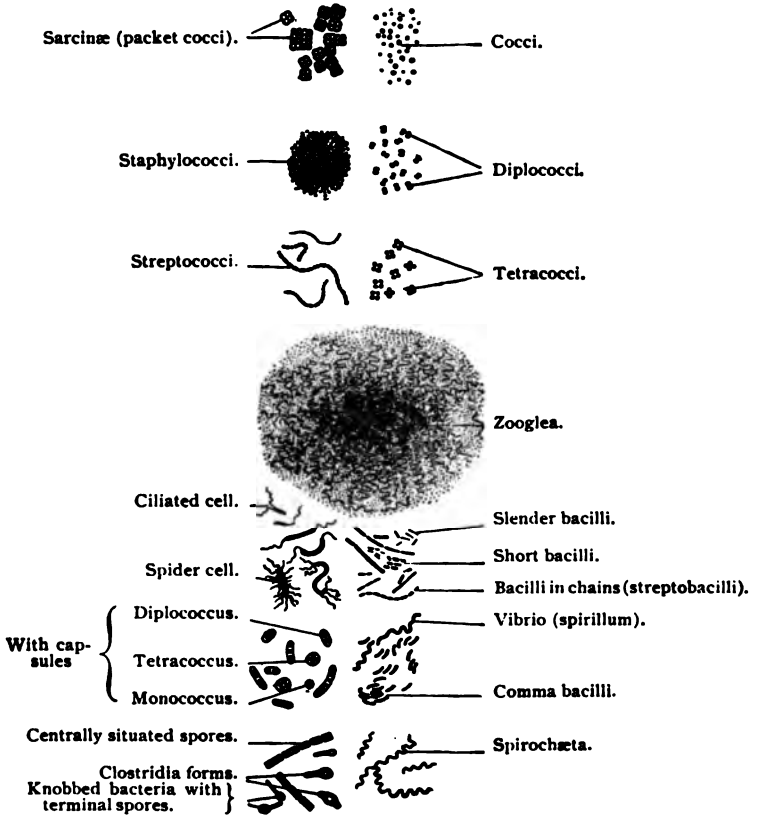

FIG. 129.—DIAGRAM ILLUSTRATING THE NOMENCLATURE OF SCHIZOMYCETES BASED UPON THEIR MORPHOLOGY.—(*After Schenk.*) × about 700 diameters.

Sarcinæ include the packet cocci: cocci arranged, in more or less cuboid shapes, as multiples of four. Each packet contains 8, 16, 32, or more units. The cocci proper include those named by the number commonly in the group, as: (*a*) Monococci, or cocci with no special arrangement or grouping; with these we include the staphylococci. (*b*) Diplococci, or cocci grouped in pairs. (*c*) Tetracocci, cocci grouped in fours. The second method of naming is by arrangement, as: (*A*) Streptococci, cocci arranged in chains; (*B*) ascococci, or encapsulated grouped cocci; (*C*) staphylococci, or cocci presumed to be arranged as grapes in a cluster. The student will fail to detect, under the microscope, the difference between the micrococci and the staphylococci. The term "zooglea" is applied to agminated masses of microbes, usually cocci, embedded in a glue-like mass of gelatinous material elaborated by the microbe. The ciliated and spider cells are flagellate bacteria. The spirochæta are flexible spirals, such as the organism of relapsing fever.

cocci arranged in irregular masses; the individual elements are embedded in a gelatin-like substance elaborated by the cocci.

Ascococci: cocci associated in circular or globular masses (zooglea) held together by a gelatinous substance. Sarcinæ: cocci arranged in packets or cubes of eight or more elements.

II. *Bacilli.*—Rod-shaped organisms, motile or nonmotile, rigid or flexible. The organism formerly described as a bacterium is included in this class.

III. *Spirilla.*—Curved or spiral filaments, rigid or flexible.

PATHOGENIC COCCI.

Gonococcus (Neisser, 1879).

Place Found.—Within the cells of gonorrheal pus.

Variety of Coccus.—Roll-shaped diplococcus, 0.8 μ to 1.6 μ in diameter.

Motility.—Nonmotile.

Growth.—Human blood-serum; smooth, thin, grayish-yellow, moist film with ill-defined margins first develops; later, forms jagged protuberances with sharply defined edges. Growth very slow. No growth on gelatin. Growth may be obtained on acid urine agar. (See p. 80.) A drop of human blood spread over the surface of a sterile agar slant also affords a medium suitable for the growth of the gonococcus.

FIG. 130.—DIPLOCOCCUS OF GONORRHEA, GONOCOCCUS.—(*Coplin and Bevan.*) × 800 diameters.

Temperature.—Optimum, 33° to 37° C. Maximum, 38° C. Minimum, 25° C.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Produces gonorrheal inflammation when inoculated upon mucous membranes; has been found in the joints in gonorrheal rheumatism and in the heart-valve in ulcerative endocarditis secondary to gonorrhea.

Demonstration.—Make spread of the discharge on cover-slip; dry and fix.

Stain with saturated alcoholic solution of methylene-blue for from five to fifteen minutes; wash with water, and then stain with saturated alcoholic solution of eosin for the same length of time. Wash in water, dry, and mount. The nucleus of pus-corpuscles, as well as the gonococci, will be stained blue, while the protoplasm of pus-cells is stained pink with eosin. Does not stain by Gram's method.

Trachomcoccus or **micrococcus of trachoma** (Sattler, 1885).

Place Found.—Conjunctiva, follicles, and inclosed follicles of trachoma.

Variety of Coccus.—Roll-shaped diplococcus.

Motility.—Nonmotile.

Growth.—May be cultivated upon gelatin, agar, blood-serum, and potato. Forms a shining, light gray film along the stab, or small globular colonies develop along the streak. Does not liquefy gelatin.

Temperature.—Optimum, 36° C.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Pathogenic only in man. Inoculation in the conjunctiva followed by the development of typical trachoma.

Stains with gentian-violet, methylene-blue, and carbolfuchsin; also other anilin dyes. Stain from five to ten minutes; wash in water, dry in air, and mount. Stains also by Gram's method.

Diplococcus Pneumoniæ (A. Fränkel, 1884).

Place Found.—In the sputum of those suffering from croupous pneumonia, severe cases of empyema, and occasionally in the exudate of cerebrospinal meningitis.

Variety of Coccus.—Diplococcus, lance-shaped. Usually associated in pairs, end to end. Five or six may be arranged in the form of a short chain. In the exudates from the body they are found in capsules, which disappear when cultivated upon artificial media.

FIG. 131.—DIAGRAM OF THE DIPLOCOCCUS OF PNEUMONIA, ILLUSTRATING RELATION OF CAPSULE TO THE CONTAINED GERM.—(*Coplin and Bevan.*)

Motility.—Nonmotile.

Growth.—Develops slowly and with difficulty upon, and does not liquefy, gelatin. Usually forms small discrete colonies with sharply defined edges and of a whitish color. Upon agar delicate, shining, semi-transparent colonies, which are almost invisible. Upon blood-serum a delicate, transparent, moist film. Nonliquefying.

Temperature.—Optimum, 35° C. Maximum, 42° C. Minimum, 24° C.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Pathogenic in mice, guinea-pigs, and rabbits. In man the cause of croupous pneumonia.

Stains with carbolfuchsin, gentian-violet, or methylene-blue; also other anilin dyes. Stain for from five to ten minutes; wash in water, dry in air, and mount.

Friedländer recommends staining the pneumococcus in tissues as follows: Make a thin section of specimen, dissolve the paraffin from it, and stain for twenty-four hours in an acid solution of

gentian-violet. This is made by taking 50 parts of a saturated alcoholic solution of gentian-violet, 100 parts of distilled water, and 10 parts of acetic acid. After staining, decolorize with a one per cent. solution of acetic acid in water for one or two minutes, dehydrate with alcohol, clear with oil of cloves, and mount.

For *staining the capsule* of the pneumococcus a thin spread of sputum is obtained, dried, and fixed by passing it through the flame. It is next placed in a one per cent. acetic acid solution for a few minutes. The superfluous acid is now drained off and the spread quickly dried in the air. Now place in a gentian-violet anilin water (p. 94) for a few seconds. Wash in water, dry, and mount. The acetic acid removes a substance that is readily stained by the gentian-violet, thus leaving in the preparation, when finished, a pale background on which the brightly stained capsules are readily detected.

Diplococcus Intracellularis Meningitidis (Weichselbaum, 1887).

Place Found.—In recent exudate of cerebrospinal meningitis.

Variety of Coccus.—Usually found in pairs and fours, and sometimes in short chains of from four to six elements.

Motility.—Nonmotile.

Growth.—Does not grow upon gelatin. Grows best on Löffler's blood-serum mixture, in which it forms smooth, round, sharply defined colonies, not over one or two millimeters in diameter. Colonies may become confluent. Does not liquefy serum. Maximum development in six days. Removals should be made every two or three days. Growth on plain agar is scanty and does not bear transplanting. Colonies on glycerin-agar resemble those on blood-serum mixture. Does not grow on potato. Scanty growth in bouillon, producing faint cloudiness with slight sediment.

Temperature.—Develops only at about 36° C.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Cause of epidemic cerebrospinal fever. Pathogenic in mice, rabbits, guinea-pigs, and dogs. Mice and rabbits especially susceptible, and die in from thirty-six to forty-eight hours after inoculation.

Stain.—Does not stain by Gram's method. Stains with the usual anilin dyes.

Demonstration.—Cultures are usually secured from fluid obtained by lumbar puncture, and while the fluid so obtained may appear, by staining methods, to contain a large number of

organisms, culture experiments would seem to indicate that comparatively few of these are viable. For this reason a relatively large quantity of fluid should be spread over the surface of the culture medium. Councilman and Wright recommend for staining sections Unna's alkaline methylene-blue solution (see p. 67), applied as follows: (1) Saturated aqueous solution of eosin, twenty minutes or longer; (2) wash in water; (3) alkaline methylene-blue (diluted), one to two hours; (1) wash in water; (5) differentiate in commercial alcohol, followed by absolute alcohol; (6) clear in xylol; (7) mount in balsam. The same method may be applied to fixed spreads.

Micrococcus * Pyogenes Aureus (Rosenbach).

Place Found.—Most frequent cause of suppuration. In pus, draff, air, and earth. This organism, probably more nearly than any other, is ubiquitous.

Variety of Coccus.—Micrococci usually about 0.8 μ in diameter. Singly, in pairs, in fours, and in short chains of several elements, though most commonly in irregular masses.

FIG. 132.—MICROCOCCUS (STAPHYLOCOCCUS) PYOGENES AUREUS.—(*Coplin and Bevan.*) ×800 diameters.

Motility.—Nonmotile.

Growth.—On gelatin the growth, after twenty-four hours, appears as a faint white streak along the line of puncture. A deep yellow or golden pigment is gradually formed, and is well developed by the third day. The gelatin is liquefied and the organisms fall to the bottom, where they appear as a deep yellow precipitate. On agar the organisms develop along the stroke, forming a thin white or slightly yellow film, opaque and irregular in outline. Later the growth assumes the characteristic yellow color. The agar frequently becomes cloudy and opaque. It is not liquefied. On plates the growth appears within from twenty-four to thirty-six hours as slightly elevated colonies with sharply defined edges. The colonies, white at first, later become a deep yellow or orange color. Grows well on blood-serum. Same characteristics as when growing on agar. On potato, white at first, later deep golden color; with age the growth becomes more succulent and develops a sour odor.

Temperature.—Optimum, 30° to 37° C.

Aerobiosis.—Facultative anaerobe.

Reproduction.—Binary division.

* The term staphylococcus is much used, particularly by surgeons, instead of micrococcus. The student should remember that the terms are interchangeable.

Pathogenesis.—When injected into the subcutaneous tissue, it produces abscess; and into the veins, pyemia. Most frequent organism in suppurative processes.

Stains with usual anilin dyes and by Gram's method.

Micrococcus Pyogenes Citreus (Passet).

In every respect it resembles the micrococcus pyogenes aureus, except that it develops a lemon-yellow pigment.

Micrococcus Pyogenes Albus (Rosenbach).

Resembles the micrococcus pyogenes aureus in every respect, except that it produces no pigment, the growth appearing as a milk-white film.

Micrococcus Pyogenes Tenuis (Rosenbach).

Place Found.—In mild, though extensive, suppurative inflammations.

Variety of Coccus.—Irrregularly grouped masses and singly, 0.9 μ to 1 μ in diameter.

Motility.—Nonmotile.

Growth.—On plates, appears as small, faint, transparent colonies, and upon agar tubes as a thin, transparent, grayish streak along the inoculation stroke. The growth is very slow.

Temperature.—Probably grows best at body-temperature.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Negative results only have been obtained from the inoculation of animals.

Stains with gentian-violet, methylene-blue, and carbolfuchsin; also other anilin dyes. Stain for from five to ten minutes; wash in water, dry in air, and mount.

Micrococcus Cereus Albus (Passet).

Place Found.—In pus.

Variety of Coccus.—Micrococci, 1.16 μ in diameter. Usually grouped in irregular masses; may occur singly and in short chains.

Motility.—Nonmotile.

Growth.—In gelatin plates the micrococci appear as small white colonies, seldom growing larger than the head of a large pin. In gelatin tubes the growth is almost wholly confined to the surface, and appears like a streak of wax with elevated irregular edges. The growth is quite rapid at a temperature of from 28° to 37° C. Does not liquefy the gelatin. On agar it presents the same characteristics. Grows well on potato and blood-serum.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Found in suppurative processes, but usually associated with one of the other pyogenic cocci.

Stains with gentian-violet, methylene-blue, carbolfuchsin; also other anilin dyes. Stain for from five to ten minutes; wash in water, dry in air, and mount.

Micrococcus Cereus Flavus (Passet).

Resembles the micrococcus cereus albus, except that it develops a yellow pigment.

Streptococcus Pyogenes (Rosenbach and Passet).

Place Found.—Erysipelatous eruptions and in pus.

Variety of Coccus.—Usually in long chains of from twenty to forty elements (streptococci), 0.4 μ to 1 μ in diameter.

Motility.—Nonmotile.

Growth.—Gelatin plates; small, circular, and finely granular colonies, which, when fully developed, are light brown in color, edges slightly elevated, and center depressed. Does not liquefy the gelatin. In tubes of agar small colonies develop on surface, especially along the inoculation stroke; later may form a thin, transparent film over surface. The growth is very slow. The organisms quickly lose their viability.

Temperature.—Optimum, 35° to 37° C.

Aerobiosis.—Aerobic.

Reproduction.—Binary division.

Pathogenesis.—Produces erysipelas and also suppuration, and is found in some cases of ulcerative endocarditis, certain cases of puerperal fever, otitis, occasionally in inflammations of serous membranes, and sometimes as a secondary infection in diphtheria and other acute infectious disease, and occasionally in chronic infectious processes, such as tuberculosis, in which it may produce acute inflammatory phenomena.

FIG. 133.—STREPTOCOCCUS OF ERYSIPELAS.—(*Coplin and Bevan.*) × 800 diameters.

Stain with usual anilin dyes and by Gram's method.

Streptococcus Erysipelatis (Fehleisen).

Probably identical with the streptococcus pyogenes.

Micrococcus Tetragenus (Koch, Gaffky).

Place Found.—In the sputum and cavities of tubercular pneumonia. Saprophytic in man.

Form of Coccus.—Tetracocci. Usually in fours; also in pairs.

Motility.—Nonmotile.

Growth.—Gelatin plates; small, white, finely granular colonies having a vitreous luster. Grows well on agar, potato, and blood-serum, forming a heavy white surface growth. The growth is

slow at first, but after from forty-eight to seventy-two hours more rapid. Does not liquefy gelatin.

Temperature.—Room-temperature.

Aerobiosis.—Facultative aerobe.

Reproduction.—Binary division.

Pathogenesis.—Fatal to mice and guinea-pigs. Field-mice and rabbits refractory. Often found in man, associated with the bacillus tuberculosis in tubercular pneumonia and chronic ulcerating pulmonary tuberculosis. To this disease, however, it bears no causal relation.

Stains with usual anilin dyes and by Gram's method.

Bacillus Diphtheriæ (Löffler).

Place Found.—Diphtheric membrane.

Form and Arrangement.—Straight or slightly curved rods, 2 μ to 4.8 μ in length, and 0.3 μ to 0.8 μ in breadth. The extremities usually stain with great intensity, while the center may remain clear, giving the organism a dumb-bell shape.

Motility.—Nonmotile.

Growth.—In tubes of gelatin small colonies develop along the puncture, and later become confluent, forming a thin gray streak. Gelatin not liquefied. Blood-serum is best adapted to the cultivation of this bacillus. (See Löffler's Blood-serum, p. 74.) Alkaline bouillon, milk, and agar are also suitable culture media. The cultures may retain their vitality for several months. A growth will develop upon potato; at first it is invisible, and only after several days does it appear as a dry, thin glaze.

Temperature.—Optimum, 37° C. Minimum, 20° C.

Aerobiosis.—Aerobe and facultative anaerobe.

Reproduction.—Entirely by fission. Spore formation does not occur.

Pathogenesis.—Inoculated on mucous membranes engenders a catarrhal, pseudomembranous, gangrenous, or other inflammation, associated with more or less systemic disturbance. A nonvirulent organism, called the pseudodiphtheria bacillus, has been described. While presenting certain morphologic and biologic differences from the virulent organism, it is generally conceded that it is but an attenuated form of Löffler's germ.

Stains with usual anilin dyes. Löffler's alkaline methylene-blue is specially adapted for staining it. (See foot-note, p. 67.) Also stains well by Gram's method.

Demonstration.—Swabs are prepared by firmly wrapping one end of a piece of wire (fourteen centimeters long and about two millimeters in thickness) with cotton, which should completely cover the end, so as to prevent possible injury when the swab is

applied. Ten centimeters from the same end a second roll of cotton is placed around the wire, sufficiently large to fit tightly into the mouth of a test-tube. The swab and test-tube are sterilized in a hot-air sterilizer. The inoculations are obtained by rubbing this swab over the affected area and then at once gently smearing the surface of a slant tube of Löffler's medium. Spreads may also be made from the swab on cover-glasses and may be fixed in the usual manner. Colonies on Löffler's medium appear within twenty-four hours. They are grayish in color, moist, round or oval in outline, slightly more elevated, and opaque at the center. Spreads from such colonies, stained with Löffler's methylene-blue, will show the organism as previously described; also as club-shaped and irregular rods. These involution forms, staining irregularly, are of great diagnostic value.

Neisser's Differentiating Stain.—Dissolve 0.5 gm. of methylene-blue (Grübler) in 10 c.c. of commercial alcohol; add to this 425 c.c. of distilled water and 25 c.c. of glacial acetic acid; stain cover-glass preparations for from one to five seconds, wash in water, and stain for five seconds in solution made by dissolving 0.5 gm. of vesuvin in 250 c.c. of boiling distilled water; wash in water, dry, and mount. This method shows to advantage the polar granules in the diphtheria bacillus; organisms not showing the polar granules are not diphtheria bacilli. The bacilli of pseudodiphtheria may, rarely, show polar granules.

The pathogenicity of the organism may be tested by subcutaneous injection of 0.5 c.c. of bouillon culture from twenty-four to forty-eight hours old. This should kill a medium-sized guinea-pig.

Bacillus Coli Communis (Emmerich).

Place Found.—In the intestinal tract of man and many of the lower animals.

Form and Arrangement.—Short rods, 1.6 μ to 3.2 μ in length, and 0.4 μ to 0.8 μ in breadth. At times they may assume an oval or spheric form. Usually arranged in irregular masses and sometimes in pairs.

Motility.—Motile.

Growth.—On gelatin plates colonies develop as small, flat, grayish points, with irregular outlines. In gelatin tubes the growth develops along the line of puncture as small, white, globose colonies, and on the surface it spreads out as a faint grayish film. The gelatin is not liquefied. Luxuriant growths develop on potatoes; in color, slightly yellowish. On blood-serum a heavy growth quickly develops. An abundant growth

will also develop on agar. In many tubes gas will be produced in abundance. Produces indol. Coagulates milk. (See table, p. 184.)

Temperature.—Optimum, about 20° to 30° C.

Aerobiosis.—Aerobic and facultative anaerobe.

Reproduction.—Fission. Spore formation not observed.

Pathogenesis.—Small injections fatal to rabbits and guinea-pigs. When localized in the tissues, engenders an intense inflammatory condition, and, according to some investigators, produces suppuration.

Stains with usual anilin dyes. Does not stain by Gram's method.

Bacillus Œdematis Maligni (Hesse, Koch).

Place Found.—Garden earth.

Form and Arrangement.—Rods from 3 μ to 5.3 μ in length, and 1 μ to 1.1 μ in breadth. The ends are usually slightly rounded. Usually they are found joined end to end, though they may form chains of from fifteen to twenty elements.

FIG. 134.—BACILLUS ŒDEMATIS MALIGNI. × 1000 diameters.

Motility.—Motile.

Growth.—On agar plates opaque white colonies develop. Frequently they appear as shining, globose bodies with liquid contents. On agar containing two per cent. of grape-sugar a profuse growth develops through the medium, imparting to it a diffuse cloudiness, most intense along the inoculation track. It grows also on gelatin, blood-serum, potato, and in guinea-pig bouillon. Liquefies gelatin.

Temperature.—Optimum, 37° C.

Aerobiosis.—Strictly an anaerobe.

Reproduction.—By fission and spore formation.

Pathogenesis.—Guinea-pigs and mice very susceptible. In man, produces extensive subcutaneous edema, beginning at the point of infection. Large quantities of gas are usually developed.

Stains with the usual anilin dyes, but not by Gram's method.

Bacillus Anthracis (Pollender and Davaine).

Place Found.—Blood of animals dying from splenic fever.

Form and Arrangement.—Rods varying greatly in size and having square ends. Length, 3 μ to 20 μ; breadth, 1 μ to 1.25 μ. They are found singly, irregularly grouped, and in long threads of many elements.

Motility.—Nonmotile.

Growth.—Grows quite rapidly upon agar, gelatin, potato,

blood-serum, and bouillon. A white growth develops quite rapidly along the line of inoculation, and from this point spreads over the surface of the media. Gelatin is liquefied, as is also blood-serum. Stab cultures show, along the needle-track, a growth that radiates in brush-like extensions into the surrounding medium, giving rise to the so-called "tree culture."

FIG. 135.—BACILLUS ANTHRACIS.—(*Coplin and Bevan.*) × 800 diameters.

Composite field showing single bacilli, also a chain, and, above, a filament with spores. There are not uncommonly more than one spore to the bacillus.

Temperature.—Optimum, 37° C. Minimum, 12° C. Maximum, 45° C.

Aerobiosis.—Aerobe; facultative anaerobe.

Reproduction.—Fission and spore formation.

Pathogenesis.—The cause of wool-sorter's disease and malignant carbuncle in man. Cattle, horses, sheep, rabbits, and many other of the lower animals are susceptible to infection.

Stains with usual anilin dyes and by Gram's method. (For spore staining see p. 96.)

Bacillus of Symptomatic Anthrax (Feser and Bollinger).

Place Found.—In fluids and secretions of animals dying of symptomatic anthrax.

Form and Arrangement.—Fine rods, 3 μ to 5 μ in length, and from 0.5 μ to 0.6 μ in breadth, and with rounded ends. Found singly and in pairs, but rarely, if ever, in threads; involution forms occur in old cultures.

Motility.—Motile; flagellate.

Growth.—Grows upon agar, gelatin, blood-serum, potato, and bouillon. Colonies in gelatin plates appear at first somewhat spheric, with irregular outlines and granular surface. When the gelatin about them becomes liquefied, they exhibit, by transmitted light, a thick, heavy center with radiating branches. On tubes of gelatin the growths become manifest in from twenty-four to twenty-eight hours. The color and general appearance are much the same as shown in plates. Considerable gas, having an acid, penetrating odor, is developed. The gelatin is liquefied.

FIG. 136.—BACILLUS OF SYMPTOMATIC ANTHRAX.—(*Coplin and Bevan.*) × 800 diameters.

Temperature.—Optimum, 37° to 40° C. Minimum, 13° C. Maximum, 70° C.

Aerobiosis.—Strict anaerobe.

Reproduction.—Spores and fission.

Pathogenesis.—The specific cause of symptomatic anthrax (black-leg or quarter evil); known to the French as "charbon symptomatique," and to the Germans as "Rauschbrand." Guinea-pigs very susceptible. Cattle, sheep, and goats susceptible. Cats, dogs, pigs, rabbits, pigeons, chickens, and ducks immune.

Stains with the usual anilin dyes, but only partly by Gram's method, requiring prolonged staining and not bearing differentiation well. (For spore staining see p. 96.)

Bacillus Pneumoniæ (Friedländer; Friedländer's pneumococcus, or, more correctly, pneumobacillus).

Place Found.—In lungs affected with croupous pneumonia.

Form and Arrangement.—Oval and short, thick rods. The oval organisms are often in pairs, with their ends in juxtaposition. When obtained from the lungs, usually incased in capsules, which are lost during cultivation.

Motility.—Nonmotile.

Growth.—Grows well upon gelatin, agar, blood-serum, and potato. On gelatin and agar in about twenty-four hours a slight grayish growth becomes visible along the inoculation streak, which later widens and produces the nail-head appearance on the surface. The gelatin becomes brownish, but is not liquefied. In a few days the growth takes on a peculiar glaze. Gas is formed.

Temperature.—Optimum, 37° C. Minimum, 14° C. Maximum, 40° C. Thermal death-point, 56° C.

Aerobiosis.—Aerobe.

Reproduction.—Fission. Spore formation doubtful.

Pathogenesis.—May occasion a croupous inflammation in man. Mice, guinea-pigs, and dogs susceptible.

Stains with the usual anilin dyes, but not by Gram's method.

Friedländer's direction for staining the capsule (spreads, properly fixed, or sections): (1) Stain in the following solution for twenty-four hours ·

Saturated alcoholic solution of gentian-violet, . . .	50 parts.
Distilled water, ...	100 "
Acetic acid, ...	10 "

(2) wash one or two minutes in one per cent. aqueous solution of acetic acid; (3) dehydrate in alcohol; (4) clear in cedar oil; (5) mount in xylol balsam.

Bacillus Pyogenes Fœtidus (Passet).

Place Found.—In fetid suppurative processes.

Form and Arrangement.—Short rods with rounded ends,

singly and in short chains. Length, 1.45 μ, and approximately 0.5 μ in breadth.

Motility.—Motile.

Growth.—Grows profusely upon gelatin, agar, blood-serum, potato, and bouillon. In twenty-four hours a light gray streak becomes visible along the line of inoculation, whence it spreads over the surface of the culture medium. Gradually the growth assumes a brown hue, becomes thicker, opaque, and shining. Produces an exceedingly malodorous gas. Gelatin not liquefied. Growth very rapid.

Temperature.—Optimum, 30° to 37° C.

Aerobiosis.—Aerobe.

Reproduction.—Spores and fission.

Pathogenesis.—Pyogenic. Rapidly fatal to mice and guinea-pigs.

Stains with usual anilin dyes and by Gram's method.

Bacillus Pyocyaneus (Gessard).

Place Found.—In green pus.

Form and Arrangement.—Short, delicate rods, 1.5 μ in length and 0.5 μ in breadth.

Motility.—Motile.

Growth.—Grows upon gelatin, agar, potatoes, and milk. On solid media a transparent film develops over the surface in about twenty-four hours. Later, it becomes a light gray or greenish color. The medium gradually becomes fluorescent. Gelatin is liquefied. Growth rapid.

Temperature.—Optimum, 26° to 37° C.

Aerobiosis.—Aerobe.

Reproduction.—Fission.

Pathogenesis.—Pyogenic, producing green pus; it is also capable of producing septicemia. As a result of abundant growth in the intestine, particularly of children, it is believed that it produces a special form of intoxication. Fatal to guinea-pigs.

FIG. 137.—BACILLUS OF RHINOSCLEROMA. × 1400 diameters.

Stains with usual anilin dyes and by Gram's method.

Bacillus of Rhinoscleroma (von Frisch).

Place Found.—Tissue from the nose of person suffering from rhinoscleroma.

Form and Arrangement.—Short rods with rounded ends and oval elements. Found singly, in pairs, and in short chains. Commonly about 1.5 μ long and 0.5 μ broad.

Motility.—Nonmotile.

Growth.—Grows upon gelatin, agar, blood-serum, and potato. In tube culture growth becomes visible in from twelve to twenty-four hours: first, as a milk-white film along the inoculation streak; later, spreads over surface of culture medium. Does not liquefy gelatin. Grows rapidly.

Temperature.—Optimum, 36° to 38° C.

Aerobiosis.—Facultative anaerobe.

Reproduction.—Fission. Spore formation doubtful.

Pathogenesis.—Specific cause of rhinoscleroma. Injected subcutaneously in mice, guinea-pigs, and rabbits, produces inflammation, suppuration, and death.

Stains with usual anilin dyes and by Gram's method.

Bacillus Mallei (Löffler and Schultz).

Place Found.—In the nasal secretions and the nodules of glanders and farcy.

Form and Arrangement.—Rods 2 μ to 5 μ long and 0.5 μ to 1.4 μ broad.

Motility.—Motile.

Growth.—Grows well on all the common culture media, but especially so upon glycerin-agar. Develops as a pale, white, moist, transparent film along the track of inoculation. Frequently such cultures show transverse striations. Does not liquefy gelatin. Old cultures on potato show a peculiar reddish-brown (chocolate or "café-au-lait") color, with discoloration on the surface of the medium.

FIG. 138.—BACILLUS MALLEI.—(*Coplin and Bevan.*) × 800 diameters.

Temperature.—Optimum, 37° C. On glycerin-agar grows at room-temperature. Maximum, 42° C. Minimum, 25° C. Thermal death-point, 85° C.

Aerobiosis.—Facultative anaerobe.

Reproduction.—Fission and spore formation.

Pathogenesis.—Specific cause of glanders. Man, horses, rabbits, guinea-pigs, and field-mice susceptible.

Stains.—Requires prolonged staining with the usual anilin dyes and bears washing poorly; is not stained by Gram's method. Usually stains irregularly.

Demonstration.—Place a small piece of infected tissue or a minute quantity of the culture in the peritoneal cavity of a male guinea-pig. Within from twenty-four to forty-eight hours testicular swelling will appear, which may be followed by abscess formation; later, the animal may develop inflammation of the nasal mucosa; swelling of the joints and characteristic nodules may be found in the viscera. The swelling of the testicle is

sufficient for preliminary diagnosis. The diagnosis of glanders may be made by the use of mallein, which is prepared in the same way as tuberculin. (See Tuberculin.) In healthy animals mallein induces no fever and but slight local disturbance, which quickly subsides. In the glandered animal it produces a sudden rise of temperature (1.5° to 2.5° C.), notable prostration, and a local swelling, which does not subside for a week or more.

Bacillus Tuberculosis (Koch).

Place Found.—In tubercular products and processes.

Form and Arrangement.—Rods slightly curved or bent, ends rounded. Length, 1.5 μ to 3.5 μ; breadth, 0.25 μ.

Motility.—Nonmotile.

Growth.—May be cultivated upon blood-serum and glycerin-agar. Upon blood-serum small, transparent, light gray colonies first develop along the inoculation streak. Later, they become

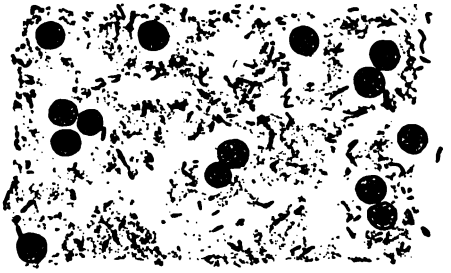

FIG. 139.—BACILLUS TUBERCULOSIS.—(*Von Jaksch.*) × 800 diameters.

confluent, forming a grayish-white growth. Upon glycerin-agar small white colonies first develop; then, after a few days, coalescing, they form a uniform yellowish-white layer, which is wrinkled or scale-like—the so-called "bread-crumb" appearance. The growth develops very slowly, requiring from two to three weeks to make its appearance on blood-serum, and from one to two weeks on glycerin-agar.

Temperature.—Optimum, 37.5° C. Minimum, 30° C. Maximum, 42° C.

Aerobiosis.—Aerobe.

Reproduction.—Fission. Spore formation probable, though involved in doubt.

Stain.—Requires prolonged staining, but bears differentiation well. Stains with the usual anilin dyes and by Gram's method. (See demonstration below.)

Demonstration (*sputum*).—Search is made for yellowish, opaque,

round particles, and, when found, a spread is made on a thin cover-glass by means of a platinum needle. The film of sputum thus obtained is allowed to dry in air or is held high over a flame until dry. To coagulate the albumin and to fix the specimen, it is passed through a flame three times. It is then covered with carbolfuchsin solution and heated for three minutes over an alcohol lamp or some distance above a Bunsen burner, not allowing the stain to boil or to become dry. Wash in water and apply a few drops of acid methylene-blue (Gabbett's counterstain) for three minutes, or until all red color has disappeared. Wash in water and mount in water, or dry and mount in balsam, and examine with a $\frac{1}{5}$-inch objective, followed by $\frac{1}{12}$-inch oil-immersion lens. The tubercle bacilli appear as short red rods, while the ground, cellular elements and other bacteria are stained blue. When a hurried diagnosis is not required, the cover-glass spread may lie in carbolfuchsin for twelve hours, without heating, and be counterstained as just described. Specimens prepared in this way retain their color much longer, and when the organisms are not found by the rapid method, the slow stain should be tried.

Gabbett's Acid Methylene-blue (counterstain):

Methylene-blue,	2 parts.
Twenty-five per cent. aqueous solution of sulphuric acid,	100 "

Ziehl-Neelsen Method for Staining Tubercle Bacilli in Tissues.— Stain the section for fifteen minutes in carbolfuchsin, which should be heated; decolorize in a twenty-five per cent. aqueous solution of nitric or sulphuric acid; wash in sixty per cent. alcohol; for contrast, stain with methylene-blue; wash and dehydrate with alcohol. Clear with oil of cloves and mount in balsam. The tubercle bacilli will be stained red, and the tissues blue.

For the *demonstration of the tubercle bacillus in the urine* the specimen should be treated as already described on page 118. The sediment so obtained is spread upon cover-glasses, and treated as previously described for sputum. A large number of covers should be examined, as the number of organisms present is often small. The smegma bacillus is less resistant to acids and is decolorized by prolonged washing in absolute alcohol; in films differentiation from the tubercle bacillus is difficult. Inoculations on animals may be necessary, and, even after inoculation tuberculoid nodules may be produced that can be differentiated from true tubercles only with difficulty.

Animals suffering with pseudotuberculosis do not react to tuberculin, and cultures obtained from the tuberculoid nodules

differ materially from the growths produced by the tubercle bacillus.

The *demonstration of the tubercle bacillus in milk, butter, etc.*, is attended with the same difficulties noted when considering urine.

Bacillus Tuberculosis Gallinarum (Bacillus of Avian Tuberculosis).—The bacillus of bird tuberculosis stains like the ordinary tubercle bacillus, but grows more readily at a lower temperature on the same media. It may be readily cultivated at a temperature of 43° C. The growth is moist and soft, not dry and crumbly. Dogs can not be infected, while comparatively large doses of the bovine organism may render them tuberculous. Recently it has been claimed that the bacillus of bovine tuberculosis may be converted into the bacillus of avian tuberculosis by placing bouillon growths of the organism in sterile collodion capsules and permitting these to remain for a variable length of time, usually months, in the abdominal cavity of a fowl. Cultures made from capsules so treated can not be differentiated from the bacillus of avian tuberculosis.

The bacillus of fish tuberculosis grows at a comparatively low temperature, 23° to 25° C., and not at 39° C.

Tuberculin.—The diagnosis of tuberculosis in animals is usually made by the injection of tuberculin, which produces, in tuberculous animals, rapid elevation of temperature lasting a few hours; this temperature reaction is associated with the formation of an inflammatory zone around the tuberculous areas. Tuberculin is prepared by growing the tubercle bacillus in large flasks containing glycerin bouillon for about six weeks, or until an abundant, thick, folded pellicle forms on the surface of the medium. The culture is then steamed for one hour, filtered through a Pasteur filter, and, if necessary, concentrated by evaporation over a water-bath. The dose depends upon the toxicity of the preparation and is determined by experiment upon animals. No reaction should occur in non-tuberculous animals.

FIG. 140.—DIAGRAM ILLUSTRATING THE FORMS OF BACILLUS TETANI.—(*Coplin and Bevan.*)

a. Spool shape. *b*. Chain form. *c*. Clubbed bacilli, with spore at one end. *d*. Club without spore. *e*. Spindle form with spore in center. *f*. Free spores.

Bacillus Tetani (Nicolaier, Kitasato).

Place Found.—Earth. In the discharge from wounds of persons having tetanus.

Form and Arrangement.—Straight, slender rods with rounded ends; irregular and involution forms occur.

Motility.—Motile, except when spore bearing.

Growth.—Grows upon blood-serum, agar, gelatin, and bouil-

lon. The most favorable medium is nutrient gelatin having a slight alkaline reaction and containing one per cent. of grape-sugar. The growth becomes visible at the end of three or four days. In gelatin stick cultures, colonies first make their appearance along the puncture below the surface. They usually coalesce, and form a branching or radiate growth. Gelatin is liquefied; a small amount of gas is generated. Does not form acid.

Temperature.—Optimum, 36° to 38° C. Minimum, 14° C. Maximum, about 42° C. Thermal death-point of spores, 100° C.

Aerobiosis.—Anaerobe and, after long cultivation, facultative aerobe.

Reproduction.—Fission and spore formation.

Pathogenesis.—The specific cause of tetanus. Man and many of the lower animals susceptible, especially guinea-pigs and rabbits.

Stains with usual anilin dyes and by Gram's method. (Stain for spores as described upon p. 96.)

Demonstration.—Make anaerobic cultures; after full development subject cultures to steam (80° C.) for one hour; this treatment usually destroys the associated bacteria. The presence of "drumstick" organisms in cultures is quite significant.

Bacillus Typhosus (Eberth, Gaffky).

Place Found.—Spleen and intestines of typhoid cadavers, feces, urine, and water.

Form and Arrangement.—Straight rods with rounded ends, 1 μ to 3 μ in length, 0.5 μ to 0.8 μ in breadth. Found singly, in irregular groups, and in cultures, forming long filaments.

FIG. 141.—BACILLUS TYPHOSUS, SHOWING FLAGELLA.—(*Gould.*) × 1200 diameters.

FIG. 142.—BACILLUS TYPHOSUS.—(*Coplin and Bevan.*) × 800 diameters.

Motility.—Motile. Numerous lateral flagella.

Growth.—Grows upon gelatin, potato gelatin, agar, potato, milk, and blood-serum. Upon agar the growth is quite rapid. It first becomes visible along the line of inoculation as a grayish-white, semitransparent film. Later on it takes a yellow or brownish cast. The growth on acid potato is significant; at first it is invisible, but imparts to the potato a moist, shining appear-

ance by the development of a perfectly transparent film. The typhoid bacillus is nonliquefying.

Temperature.—Optimum, 36° to 38° C. Will grow at room-temperature. Thermal death-point, 60° C.

Aerobiosis.—Aerobe, facultative anaerobe.

Reproduction.—Fission.

Pathogenesis.—Specific cause of typhoid fever.

Stains with usual anilin dyes, but not by Gram's method.

One of the most difficult differentiations that a bacteriologist may be called upon to make is between the bacillus typhosus and the bacillus coli communis. The following is a modified and extended form of a table from Pearmain and Moor, presenting the points of difference between the bacillus typhosus and the bacillus coli communis :

Media and Tests.	Bacillus Typhosus.	Bacillus Coli Communis.
Gelatin plates.	The colonies on the surface form large grayish-white expansions with irregular edges, and after a time become somewhat yellowish-brown. The deep colonies are darker, with regular edges. Under a low power the colonies exhibit a characteristic woven structure. The gelatin is not liquefied.	The colonies are round and oval, with smooth-rimmed margins. The surface colonies form dirty-white expansions that, on magnification, exhibit a furrowed appearance. The colonies later become dirty yellowish-brown in color. The gelatin is not liquefied.
Gelatin streak culture.	Produces a grayish-white expansion with irregular edges. The growth has a tendency to keep to the inoculation streak, and often has a bluish iridescence.	Dirty yellowish-white expansion, which spreads all over the surface of the medium, and often has a bluish iridescence when viewed by transmitted light.
Gelatin shake culture.	No gas bubbles.	Copious formation.
Agar streak culture.	Grayish-white expansion, which covers the surface of the medium.	Dirty yellowish-white expansion, which spreads over the surface of the medium.
Potatoes.	Generally a faint grayish-white growth; the growth varies, however, on different potatoes.	Slimy yellowish growth.
Milk.	Turns faintly acid. No coagulation takes place.	Curdled after one to three days.
Broth.	Rendered turbid, and gives no indol reaction.	Rendered turbid, and gives a well-marked indol reaction after from twenty-four to forty-eight hours.
Formalin broth (1 : 7000).	No growth.	Growth.

Media and Tests.	Bacillus Typhosus.	Bacillus Coli Communis.
Elsner's differentiating medium.*	Growth rarely apparent under forty-eight hours. Colonies small, finely granular, shining, looking not unlike droplets of water.	Growth in twenty-four hours. Colonies large, coarsely granular, brownish, and growing more rapidly.
Widal reaction.	Positive reaction with blood-serum from a typhoid patient or an animal immunized against typhoid bacillus.	No reaction in either case.
Melted gelatin, in incubator.	Uniform clouding.	Flakes or flocculi throughout the tube.
Indol.	None produced.	Present in bouillon cultures.
Neutral-red agar.†	No fluorescence.	Fluorescence may be present. Reaction not constant.
Thermal death-point.	56° C.	60° C.
Pyogenesis.	Not pyogenic.	Pyogenic.

Bacillus of Influenza (Pfeiffer, Canon).

Place Found.—In bronchial secretion and nasal mucus, and, although less commonly, in the blood of persons suffering from influenza.

Fig. 143.—Bacillus of Influenza. × 1000 diameters.

Form and Arrangement. — Small rods, 0.5 μ to 0.8 μ in length, and 0.2 μ in breadth.

Motility.—Nonmotile.

Growth.—Grows only on special media and requires frequent transplantation. (See demonstration.)

Temperature.—Optimum, 36° to 38° C. Does not grow below 28° C. Thermal death-point, 60° C.

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* Elsner's differentiating medium:

Selected potato, thoroughly cleaned, ... 0.5 gm.
Water, ... 1.0 liter.

Boil thoroughly, mashing the potato in order that the salts may be extracted and a part of the starch dissolved. Sufficient gelatin is added to render the medium solid: usually ten per cent.; after solution, sodium hydroxid is added until the reaction is but *faintly acid*, using litmus as the indicator; clarify, filter, and prepare as usual. To this medium one per cent. of iodid of potassium is added. The plates are made in the usual way. Original article, "Zeitschr. f. Hyg.," Bd. XXI, 1.

† To apply test, add four drops of concentrated aqueous solution of neutral red to 10 c.c. of liquefied agar and 0.5 c.c. of twenty-four-hour bouillon culture of bacillus typhosus.

Aerobiosis.—Aerobe.

Reproduction.—Fission. Spore formation not observed.

Pathogenesis.—Specific cause of influenza. Men, apes, and rabbits very susceptible.

Stains with ordinary anilin dyes, but not by Gram's method.

Demonstration.—Smear the surface of agar slants or agar in Petri dishes with fresh sterile blood; inoculate surface with blood of influenza patient or nasal or bronchial mucus, which may be diluted with sterile water. The essential requisite to growth is blood, not blood-serum; and any similar organism growing on usual media may be excluded. The developed colonies are small (they may require a lens for demonstration), moist, dew-like drops, which do not coalesce.

Bacillus Pestis (Bacillus of Bubonic Plague).

Place Found.—The organism is most abundant in the affected lymph-nodes, which, in advanced cases, are crowded with bacilli. It is also present in the spleen and is occasionally found in the blood of patients suffering from the disease. The stools also contain the organism.

Form and Arrangement.—Small spindle-shaped bacilli (2.3 μ by 1.7 μ), arranged in sharply and repeatedly bent chains; also long and short forms, with intermediate stages, and sometimes with rounded ends. In the glands polar staining sometimes creates an appearance resembling diplococci.

Motility.—Varies as to motility, but possesses flagella.

Growth.—On agar forms moist, white growth; on potato, scanty growth. In bouillon the growth should not be disturbed, but placed on a perfectly steady shelf; twenty-four to forty-eight hours after inoculation flakes appear underneath the surface, forming small islands of growth (Haffkine). Produces indol. Does not liquefy gelatin and may show a tree-like growth resembling the anthrax bacillus. Does not coagulate milk. The best medium is an alkaline solution of peptone containing one or two per cent. gelatin. It causes acid formation.

Temperature.—Optimum, 37° C. Thermal death-point, 76° C. for thirty minutes, or a much more brief exposure to 100° C.

Aerobiosis.—Aerobe and facultative anaerobe.

Reproduction.—By fission.

Pathogenesis.—Pathogenic in man, small laboratory animals, as rats, guinea-pigs, and rabbits; pigeons are exempt.

Stains with usual anilin dyes, but not by Gram's method.

Demonstration.—A drop of serum obtained by hypodermic puncture from one of the swollen lymphatic glands will usually show the organisms in abundance. In addition to the differen-

tiating points already given, an inoculation made on agar containing three per cent. of salt, and incubated at a temperature of 37° C., develops involution forms resembling yeasts. As this development takes place within twenty-four hours, it constitutes an important test. The ease with which rats may be infected and the characteristic glandular involvement of the lymph-nodes could be utilized to advantage.

Bacillus Lacunatis (Morax-Axenfeld).

Place Found.—Found in the diplobacillary conjunctivitis of man.

Form and Arrangement.—Rods about 2 μ in length and 1 μ in width, arranged in pairs placed end to end, and sometimes in short chains of from four to six elements. In cultures the organism is pleomorphic, growing as short diplobacilli that can not be differentiated from diplococci, and also in chains such as previously described. By the end of one week of cultivation many involution forms occur.

Motility.—The organism is nonmotile, and flagella have not been demonstrated.

Growth.—When first removed from the eye, it can be successfully grown only on serum or in media containing serum, and at a temperature approaching 37° C. In streak cultures on serum tubes a moist, shining growth occurs along the line of inoculation. The solidified serum is gradually liquefied, forming a furrow, which at first extends in depth only, but later widens. Smear cultures develop as individual colonies, which pit the serum. After cultivation through a series of serum tubes the organism may, in some instances, be grown upon agar, where it then forms "translucent, discrete colonies, like dewdrops."* In bouillon containing one-third serum a turbidity quickly develops, which is not lessened by the occurrence of a grayish-white precipitate on the sides and bottom of the tube. The organism requires frequent transplantation.

Temperature.—Optimum temperature, 37° C.; does not grow below 30° C. or above 40° C. Thermal death-point, 56° C.

Aerobiosis.—The organism is an obligate aerobe, and dies as a result of absence of oxygen.

Reproduction.—By fission. Spore formation has not been demonstrated.

Stain.—Stains slowly but clearly with the usual dyes. Stains best with an aqueous solution of *Bleu de Roux.* The reaction

* For careful study of this organism see paper by J. W. Eyre, M. S., M. D., in the "Journal of Pathology and Bacteriology," vol. VI, No. 1, May, 1899.

of Gram's method is peculiar, partial discoloration taking place; the staining is never characteristically that of Gram's method. This peculiarity is to be utilized in identifying the organism.

Pathogenesis.—Is not pathogenic in lower animals; on the human conjunctiva Morax, Axenfeld, and Eyre have produced characteristic inflammation of the conjunctiva.

Demonstration.—Cover-glass smears are stained in the usual way and by Gram's method; the organism may be identified by points already mentioned.

BACILLI NOT CULTIVATED OUTSIDE THE BODY.

Bacillus Lepræ.

Place Found.—In leprous lesions.

Form and Arrangement.—Rods resembling the tubercle bacillus. Usually, they are from 4 μ to 6 μ in length and 0.6 μ in breadth.

Motility.—Nonmotile.

Growth.—Bordoni-Uffreduzzi has obtained growths of what he believes to be the lepra bacillus upon blood-serum containing peptone and glycerin. The India Leprosy Commission claims to have obtained cultures of the lepra bacillus upon blister-serum. As the organism cultivated by Bordoni-Uffreduzzi greatly differs from the lepra bacillus in leprous lesions in both size and shape, its specific character may be doubted. Carasquilla, Spronck, and Campana also claim to have successfully cultivated the bacillus lepræ. From their descriptions it would appear that the organisms cultivated are dissimilar, and hence the claim of successful cultivation should await confirmatory demonstration before being fully accepted. The possibility, or, indeed, the probability, of successful cultivation must be admitted.

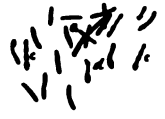


FIG. 144.—BACILLUS OF LEPROSY.—(*Coplin and Bevan.*) × 800 diameters.

a. Mature bacilli. *b,c,c.* Beaded bacilli. *d.* Slightly curved forms.

Reproduction.—Fission, and possibly spore formation.

Pathogenesis.—Specific cause of leprosy in man.

Stains with usual anilin dyes and by Gram's method. Like the tubercle bacillus, the bacillus lepræ stains with difficulty, but, once stained, retains the stain, so that, as in tuberculosis, the differentiation from other organisms is largely effected by bleaching one stain out, as carbolfuchsin, and after-staining with a second stain, as methylene-blue, the bacillus of leprosy retaining the first stain and associated bacteria the other.

Demonstration.—Bacillus lepræ resembles the tubercle bacillus in many particulars, but may be differentiated by the absence of pathogenicity in lower animals and inability to cultivate it.

Bacillus of Syphilis (Lustgarten).

Place Found.—Syphilitic secretions and lesions.

Form and Arrangement.—Straight and curved rods, 3 μ to 7 μ in length, and closely resembling the tubercle bacillus. Their outlines are irregular and their ends bulging.

Reproduction.—Fission. Spore formation probable.

Pathogenesis.—Claimed by Lustgarten to be the specific cause of syphilis.

FIG. 145.—BACILLUS SYPHILIDIS.—(*Lustgarten.*) × 1000.

Growth.—Has not been successfully cultivated.

Stain.—Tissues are stained as follows (Lustgarten's method): (1) Anilin-water gentian-violet (p. 94), twenty to twenty-four hours; (2) wash in alcohol, two or three minutes; (3) aqueous solution potassium permanganate (1.5 per cent.), ten seconds; (4) very dilute aqueous solution of sulphuric acid, two seconds; (5) aqua destillata. Repeat the last three procedures until the section is colorless. Wash in alcohol, clear in oil of cloves, and mount.

SPIRILLA CULTIVATED OUTSIDE THE BODY.

Spirillum Proteus, Spirillum of Finkler-Prior.

Place Found.—Intestinal canal and dejecta from patients with cholera nostras.

Form and Arrangement.—Curved rods from 0.6 μ to 2.5 μ in length, 0.5 μ to 0.6 μ in breadth; resembles the spirillum of Asiatic cholera, but the "commas" are longer and thicker and not so uniform in diameter, the central portion being thicker than the pointed ends. The spiral filaments are not numerous, and are usually short.

Motility.—Motile; possesses a single flagellum at one end.

Growth.—Grows on agar, gelatin, blood-serum, potato, and bouillon. On agar a moist, thick, slimy layer is quickly developed. On gelatin plates, at the end of twenty-four hours, small, white, punctiform colonies are seen, which cause a rapid liquefaction of the gelatin. In gelatin stick cultures the liquefaction progresses rapidly, at the end of forty-eight hours assuming the shape of an old stocking, and rapidly progressing to complete liquefaction. On blood-serum the growth is rapid, and causes liquefaction of the medium. On potato it produces a slimy,

grayish-yellow, glistening layer. Coagulates milk. Does not form indol.

Temperature.—Ordinary room-temperature.

Aerobiosis.—Aerobe and facultative anaerobe.

Reproduction.—By fission.

Pathogenesis.—Pathogenic for guinea-pigs when injected into the stomach by Koch's method. Is not the specific cause of cholera nostras. *Stains* with usual anilin dyes.

Spirillum Tyrogenum (Deneke).

Place Found.—Old cheese.

Form and Arrangement.—Curved rods and long, spiral filaments resembling spirilla of Asiatic cholera. The diameter of the commas is uniform throughout. The turns in the spiral filaments are longer and closer together, and the diameter of the curved segments is less than that of the cholera spirillum.

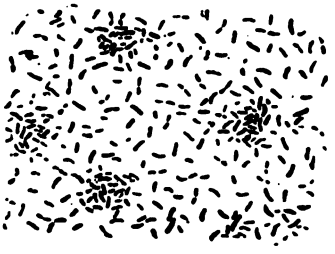


FIG. 146.—SPIRILLUM TYROGENUM.—(*von Jaksch.*) × 900 diameters.

Motility.—Motile, possessing a single flagellum.

Growth.—On agar, gelatin, potato, and bouillon. On agar thin, yellowish layer forms along the inoculation streak. On gelatin plates small, yellow, punctiform colonies are developed that have a sharp outline, but when liquefaction commences, the sharp outline disappears. In gelatin stick cultures liquefaction occurs along the whole line of puncture, the spirilla sink to the bottom as a coiled mass, while a thin, yellowish layer forms upon the surface. On potato a yellow layer is usually developed.

Temperature.—Ordinary room-temperature.

Aerobiosis.—Aerobe and facultative anaerobe.

Reproduction.—By fission.

Pathogenesis.—Pathogenic for guinea-pigs when injected into the stomach by Koch's method.*

Stains with usual anilin dyes.

Spirillum of Asiatic Cholera (Comma Bacillus) (Koch).

Place Found.—In the intestinal canal and feces in cholera.

Form and Arrangement.—Short, comma-like elements; also U and S forms and long, spiral filaments.

* The stomach is rendered alkaline by carbonate of potassium before the introduction of the organism.

Motility.—Motile. Commonly possesses a single terminal flagellum.

Growth.—Grows upon gelatin, agar, blood-serum (which it liquefies), potato, and bouillon. The growth on gelatin is most characteristic. In gelatin plates the surface at first presents an appearance resembling that produced by sprinkling the medium with delicate glass splinters, an appearance that is lost with beginning liquefaction. The gelatin plate should be kept at 22° C.; in about twenty-four hours liquefaction becomes evident, and usually progresses so that in a few days the entire plate is liquefied. Under the microscope the beginning colonies are granular with irregular borders, and white or yellowish-white in color. In stab cultures the growth begins at the surface and proceeds along the line of puncture. Liquefaction begins at the surface and accompanies the growth along the course of the needle-track. The area of liquefaction presents a funnel-like appearance, and an air-bubble is usually observed in the broad, expanding portion of the funnel. Milk is not coagulated.

FIG. 147.—SPIRILLUM OF CHOLERA.—(*Coplin and Bevan.*)
A diagram illustrating the formation of comma-shaped segments from the breaking-up of spiral forms.

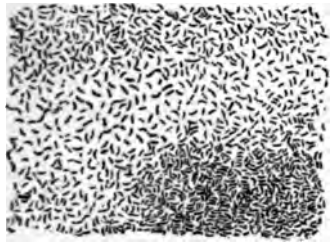


FIG. 148.—SPIRILLUM OF ASIATIC CHOLERA.—(*von Jaksch.*) × 500 diameters.

Temperature.—Optimum, 37° C. Minimum, 14° C. Maximum, 42° C. Thermal death-point, 55° C.

Aerobiosis.—Aerobe, facultative anaerobe.

Reproduction.—Fission and spore formation (?) (arthrospores).

Pathogenesis.—Specific cause of Asiatic cholera in man. Asiatic cholera has been experimentally produced in guinea-pigs with this spirillum.

Stains with usual anilin dyes, but not by Gram's method.

SPIRILLUM NOT CULTIVATED OUTSIDE THE BODY.

Spirillum of Relapsing Fever (Obermeier).

Place Found.—In the blood of relapsing fever patients during the fever paroxysms.

Form and Arrangement.—Delicate, flexible, spiral, or wave-like

filaments, with pointed ends. Their length is from 16 μ to 60 μ, and their breadth about 0.1 μ. The number of complete spirals in one organism may be from ten to fifteen.

Motility.—Very actively motile.

Reproduction.—Fission.

Pathogenesis.—Specific cause in man of relapsing fever. Monkeys are susceptible.

Stains with usual anilin dyes, but not by Gram's method.

Demonstration.—The organisms are present in the blood in large numbers during the crisis. They are less abundant just before the occurrence of the crisis, and after it is past they disappear rapidly. They are not present in the peripheral circulation during the nonfebrile period. In order to demonstrate the presence of the organism in the blood, the finger or lobe of the ear is properly cleansed, disinfected, and pricked by a needle. (See Technic of Blood Examination, chap. I, part III.) A drop of blood is received on a slightly warmed slide and a cover-glass is at once applied. As soon as the blood flows near the margin of the cover-glass a ring of oil or vaselin should be painted around the cover-glass in order to prevent too rapid drying during the progress of the examination. As the organism possessed a transverse diameter approximately that of the cholera spirillum, it will be necessary to conduct the examination with high powers. The presence of spirilla is indicated by the agitation of the corpuscular elements. At first the spirals may be too active to be readily focused upon, but in a short time they become sufficiently quiet to permit examination. Just before and during the crisis the number of spirilla may approach one organism for every twenty erythrocytes. After the disappearance from the peripheral circulation Metschnikoff has succeeded in demonstrating them in the splenic pulp. In moist films or in suspension in normal salt solution the motility may be evident for twelve hours or longer. The organism is evidently destroyed by a comparatively low temperature, a fact which has been taken to indicate the absence of spores. Dry films, prepared as described in the chapter on The Blood, may be stained as already directed for other bacteria. (See p. 93.)

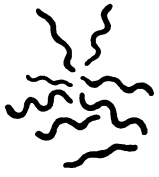


FIG. 149.—SPIRILLUM OF RELAPSING FEVER (SPIROCHÆTA OBERMEIKRI.—(*Coplin and Bevan.*) × 800 diameters.

ANIMAL PARASITES.

Sporozoa, psorosperms (gregarinidia), are animal parasites belonging to the protozoa. **Coccidia** are oval, egg-shaped organisms, the smallest measuring from 2.5 μ to 4 μ in diameter, while the largest, fully developed cell may attain a long diameter of from 26 μ to 28 μ. The transverse diameter of the ovoid is usually a little more than half its length. During the development of the morbid processes with which coccidia are commonly associated the parasite is usually found within the epithelial cell. In the earlier stage of development the epithelial cell (for example, the tall, cylindric, epithelial cell of the bile-duct) remains *in situ;* later, it is thrown off and lies free in the cavity. During the intracellular development of the organism a vesicular structure resembling a nucleus is seen near the center of the parasite; by some this is believed to be the nucleus. There is a suggestion of a cuticular membrane. After rupture, the epithelial cell disappears by disintegration, and the contents of the cuticular membrane, or pseudocapsule of the parasite, contracts into a spherule. The later stages of development are usually not observed in the morbid processes with which the organism is associated, but occur when the coccidia are exposed to a suitable temperature with a sufficient quantity of moisture. Under such conditions the spheric mass previously mentioned splits up into *psorosperms*, or *spores*, each sphere producing four of the new bodies. The spores, or psorosperms, or sporules, acquire a membranous envelop, inside of which the sporule assumes a form suggestive of a rod bent as a crescent—the so-called *sickle-shaped sporule*. Here the process of evolution is again arrested. Introduction into a suitable host is followed by the digestion of the cuticular membrane surrounding the sporule, after which the young parasite enters the epithelial cell of the intestine, bile-duct, or other structure, where the cycle of development is completed as already indicated. The demonstration of the *coccidium perforans* as a distinct member of the group does not seem to be complete, so that the majority of observers are inclined to regard it as but one form of the *coccidium oviforme*.

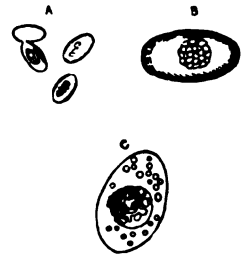


FIG. 150.—COCCIDIUM OVIFORME FROM THE HUMAN LIVER.—(*After Leuckart.—Gould.*)
A. × 200 diameters. B, C. × 800 diameters.

In the lower animals a number of diseases are produced by members of this group; coccidial disease of the liver in rabbits affords an opportunity to study the **coccidium oviforme,** to which the disease is due. A similar cystic lesion occurs in the liver of man, the cysts containing coccidia. Occasionally, the coccidial masses resemble tubercles, solid, fibrous, or caseous areas. While most common in the liver, the spleen, kidney, and ureter may be involved.

Molluscum contagiosum, also known as contagious epithelioma, is a disease occurring in the skin, and showing, as its name indicates, a certain contagious element. It sometimes spreads from nurse to infant; families may show infection, and occasionally epidemics occur in hospital wards. The molluscum nodule rises rather abruptly from the skin, and may, in rare cases, be pedunculated; it rarely reaches a transverse diameter of five millimeters, although it may be much larger. The surface is usually flat, or it may be slightly umbilicated, and, in most instances, contains a hair, more or less centrally placed. The center of the nodule contains caseous material, which can usually be readily expressed. The number of nodules varies: sometimes they are abundant, and in other instances comparatively few are seen. They may occur anywhere on the cutaneous surface, but are more frequent on the back, face, and neck, and around the genital orifices and the anus.

Properly fixed and stained sections show marked proliferation of the rete Malpighii, with degenerative changes resembling caseation. The smaller coccidial bodies are situated in the third or fourth row of epithelial cells, counting from the corium outward. They are first noted within the epithelial cells; later, by enlargement, they displace the nucleus and eventually become more conspicuous than the epithelial cell. That they are the specific cause of the disease is questioned. Their constant presence, however, and the fact that no other satisfactory explanation of the morbid process has been forthcoming, have led many observers to regard them as the etiologic factor.

The alleged coccidial origin of carcinoma will be referred to when considering the etiology of tumors.

Cercomonas intestinalis, length 10 μ to 12 μ, pear-shaped, with two terminal filaments, one of which is rigid, the other motile, by the action of which the parasite moves. In addition to the terminal filaments there are three tentacles on each side. The parasite is found in the stools during life and in the intestine postmortem. A diseased condition of the intestinal mucosa

seems necessary before this parasite will thrive in the intestine; but when once present, it induces diarrhea.

Closely resembling the preceding is the **trichomonas intestinalis,** which differs in having a disc anteriorly supplied with cilia. The *trichomonas vaginalis* resembles the foregoing; it is, however, smaller.

Amebæ belong to the rhizopodia. A number of forms have been described, the most important of which seems to be the **amœba coli,** associated with dysentery and hepatic abscess. As seen in stools, amebæ are oval in outline, 12 μ to 35 μ in diameter; while living and in the fresh state, motile. The nucleus, when present, is round or ovoid; the perinuclear protoplasm is granular, and often contains vacuoles and included blood-cells, pus-cells, bacteria, and granules. It would appear that proliferation by direct division is possible, Harris having observed the process.

Amebæ have been found in the stools from dysentery, in the intestinal wall, in hepatic abscess secondary to dysentery, in the pus from abscess of the lower jaw, and in the urine in inflammation of the bladder.

Demonstration.—A satisfactory demonstration of the parasite, particularly in the hands of the novice, demands that he should see it send out pseudopodia: he should observe active movement. In order to do this, it is necessary to have the material reasonably fresh. In the case of feces, admixture with urine is to be avoided. A drop of the suspected material is placed upon a slide and a cover-glass applied. The slide may be gently warmed, or the microscope may be kept in a reasonably warm place, under which conditions movement will be more active. Fresh specimens may be best stained by mixing with the suspected material, placed upon a slide, a drop of a watery solution of toluidin-blue. This reagent acts as a fixative and at the same time stains the amebæ intensely and rapidly. Pieces of tissue are best fixed in corrosive sublimate, embedded in paraffin, and the sections stained in eosin, followed by toluidin-blue for twenty or thirty minutes; wash and differentiate in alcohol, clear in cedar oil or xylol, mount in balsam.*

Flukes.—Certain forms of these are common in sheep. In man they infest the alimentary canal, or wander into ducts or canals emptying into it. The liver flukes: **distoma lanceolatum** is 7 to 10 mm. in length, 1.85 to 2.25 mm. wide; the **distoma hepati-**

* See remarks on the use of anilin dyes, p. 66; also toluidin-blue, p. 67; eosin with toluidin-blue, and differentiation of anilin dyes, pp. 67 and 68.

cum, 15 to 32 mm. in length, 8 to 20 mm. wide; the **distoma crassum,** 5 cm. in length; and the forms apparently so abundant in Japan, the **distoma endemicum** and **distoma perniciosum,** infest the duodenum and jejunum or invade the bile passages, producing cholangitis, jaundice, hepatic enlargement, and sometimes ascites. The irritation is not uncommonly associated with bacterial infection, which eventually proves fatal.

A form of hematuria—**endemic hematuria** of Egypt—is due to the blood fluke, **bilharzia hæmatobia** (**distoma hæmatobium**). The female is from 15 to 20 mm. in length and 0.1 to 0.2 mm. in diameter, and inhabits the portal vein and the veins of the spleen, mesentery, kidney, and bladder. The eggs are oval, possessing a spicule, which may be located at one end

FIG. 151.—DISTOMA HEPATICUM.

FIG. 152.—BILHARZIA HÆMATOBIA, MALE AND FEMALE, THE LATTER IN THE CANALIS GYNÆCOPHORUS OF THE FORMER. —(*After Leuckart.—Gould.*)

or at the side. They measure 0.12 mm. by 0.04 mm., and may be found in the liver, intestine, mesentery, and vascular plexus of the bladder, rectum, etc. Inflammations occur in the ureter and bladder, and also in the rectum; the inflammatory exudates contain ova, and ova may also be found in the submucosa of the area involved. Ulcerations sometimes develop, followed by cicatrization, which may induce stricture or other deformity. There may be marked interference with nutrition, and, in addition to the blood in the urine, chyluria may occur.

Distoma ringeri, distoma pulmonale, or bronchial fluke, is the cause of the parasitic hemoptysis endemic in China and Japan. The parasite is ovoid, 8 mm. to 10 mm. long, 3 mm. to 6 mm. wide. The eggs are yellowish, thin-shelled, and from 0.08 mm. to 0.1 mm. long, by 0.05 mm. broad. The parasite

inhabits small cavities situated at the periphery of the lung and communicating with the bronchi. It has been found in the lungs of tigers. The sputum resembles that of tuberculosis, and the associated hemoptysis further complicates the diagnosis ; finding the eggs, or occasionally the parasite, readily clears up the diagnosis.

Ascarides, or Round Worms.—The *ascaris lumbricoides* is a yellowish or yellowish-brown worm, varying in length : the female measures about 15 cm. to 30 cm. ; the male, 9 cm. to 20 cm. The worm is striated transversely with four longitudinal bands. Round worms are most common in children, occupying the upper portion of the small intestine, from which they may wander into the bile-ducts, stomach, esophagus, nose, Eustachian tube, and larynx. The number in any case varies ; rarely are they present in large numbers. The ova are ellipsoid, 0.06 mm. in their longest diameter, with a dense enveloping membrane.

FIG. 153.—ASCARIS LUMBRICOIDES AND EGGS.—(*Coplin and Bevan.*)

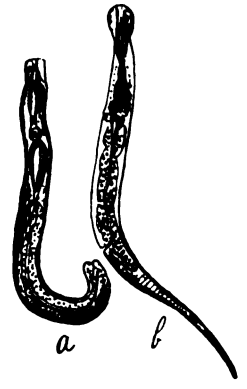


FIG. 154.—OXYURIS VERMICULARIS.—(*Coplin and Bevan.*)
a. Female. *b*. Male.

Oxyuris vermicularis, *threadworm* or *pinworm*, inhabits the colon and rectum, occasionally in the female invading the vulva and vagina. The female parasite is from 8 mm. to 12 mm., and the male 3 mm. to 6 mm. in length. Eggs are 0.05 mm. long by 0.025 mm. thick, and possess a thin shell, which offers some protection to the contained embryo when subjected to the influ-

ence of drying. The parasite wanders from the anus and provokes violent itching, which not uncommonly leads to the individual injuring the surrounding parts by active scratching, even lacerating the skin, thereby favoring bacterial infection and subsequent inflammatory disturbances.

Trichina Spiralis.—Infection by this parasite occurs by ingesting trichinous flesh. In the muscle the parasite, in the form of its embryo, will be seen as a coiled-up worm 0.05 mm. in length, surrounded by a capsule that at first is translucent, later becoming opaque, and eventually calcareous. If meat containing the embryo be eaten, the capsule is digested in the stomach, the embryo liberated, and its final development into the adult worm completed in the small intestine. The fully developed female trichina measures 3 mm. to 5 mm., the male about half as much. The embryos liberated in the intestine wander into the mucosa, penetrate the wall of the intestine, and become widely disseminated throughout the organism. The destination of the worm seems to be in the muscles; here it coils up, and is surrounded by a capsule partly produced by the reaction of the surrounding tissue. The changes that this capsule undergoes have already been noted. *Trichiniasis* is the term applied to the symptoms and lesions observed at the time of dissemination of the embryo. It is estimated that from 1000 to 2000 embryos may be hatched by a single female trichina. The dissemination of these by the route previously indicated may be associated with fever, muscular pains, more or less edema, and even paralysis. A small percentage of the cases terminate fatally. A recent and important contribution to the diagnosis of trichiniasis is the discovery of the enormous increase of the cosinophile cells in the blood.

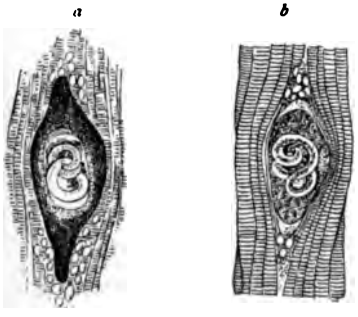


FIG. 155.—TRICHINA SPIRALIS.—(*After Leuckart.*)
a. Encapsulated. *b*. Same with calcific capsule.

Demonstration.—This may be accomplished by teasing the suspected muscle as follows: Clean a slide thoroughly and breathe upon its surface, thereby slightly moistening it; upon the moistened surface lay a fragment of the muscle to be examined; with needles tear the fragment to pieces;* add a

* This procedure is technically known as "teasing" the specimen.

drop of glycerin and a cover-glass; examine with a ½-inch or ¼-inch objective. In order to make the specimen permanent, wash out the glycerin with water, dehydrate with alcohol, clear in creasote or oil of cloves, apply balsam, and cover. The fragment of muscle may be obtained by incision, using cocain as a local anesthetic, or it may be removed by a punch or harpoon.

Anchylostoma duodenale, strongylus, or **dochmius duodenalis** is associated with certain forms of anemia and Egyptian chlorosis. The male is about 8 mm. in length, with a distinct bursal enlargement at the tail end. The female is much the larger, measuring, not uncommonly, 18 mm. By a series of tooth-like hooks with which the mouth is provided the parasite attaches itself to the mucous membrane of the duodenum. Inflammation of the intestinal mucosa results, and, in some cases, this may assume a hemorrhagic form; profound anemia is one of the most constant associated phenomena. The profound disturbances of nutrition that mark the severe cases of *anchylostomiasis* are brought about partly by the loss of blood induced through the wounding of the duodenum, partly by the associated inflammatory processes, which may not be marked, and possibly, to a certain extent, by the absorption of metabolic products elaborated by the parasite.

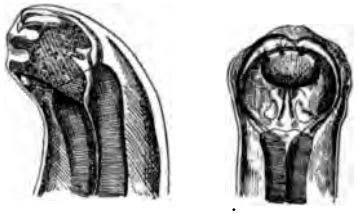


FIG. 156.—CEPHALIC EXTREMITY OF DOCHMIUS DUODENALIS, PROFILE AND FRONT VIEW.—(*After Leuckart.—Gould.*)

Infection occurs by drinking polluted water. In Egypt, Italy, Russia, and the South American States the inhabitants not uncommonly suffer, but in North America but little is known of the parasite. The recognition of the condition during life is often effected by finding the ova in the stools. The ova are about 0.05 mm. in diameter, egg-shaped, with a thin enveloping membrane.

Filaria.—In the lower animals filaria are not uncommon, but in man only a few forms of the parasite have been identified with disease. The **filaria sanguinis hominis,** so constantly associated with chyluria, hematochyluria, lymph-scrotum, and a condition resembling elephantiasis, is probably the most important. The male is small, and is rarely found. The female is a thread-like worm, 4 cm. in length, and 0.25 cm. in diameter; the head is club-like; about one millimeter behind the head is the opening of the vagina, which terminates in a bifid uterus, extending back-

ward almost the entire length of the parasite, and crowded with embryos in all stages of development. An alimentary canal runs the entire length of the parasite.

The worm inhabits the lymphatics, into which it pours an enormous number of embryos. These are nearly 0.25 mm. in length, 7 μ in thickness, about the diameter of a red blood-cell, thus permitting their transfer from point to point in the circulation, to which they gain ingress through the lymphatics. Their presence in the peripheral blood is peculiar, in that it is cyclic, appearing only in the night or during sleeping-hours. In most cases they can not be found in the day, but in individuals who sleep during the day the parasites can then be found. Manson expresses the opinion that the nocturnal appearance of the parasite is due to the fact that it adapts its habits to those of the mosquito, which

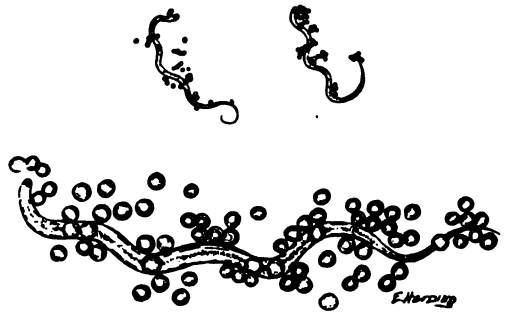


FIG. 157.—FILARIA EMBRYO.—(*From F. P. Henry's case.*)
The two embryos shown above were drawn from ⅓-inch objective; the lower from ¼-inch objective. Red blood-cells are introduced for comparison.

he regards as an intermediary host. At the autopsy of a suicide, at 8.30 A. M., the filaria were found in the vessels of the lung and myocardium, and but few in the liver, spleen, or kidney. If, at the appropriate time, a drop of blood be drawn and examined in the fresh condition, but little difficulty will be found in detecting the embryo parasite: the movements are rapid, and the enveloping membrane or shell is delicate, transparent, and so elastic that it in nowise impedes the movements of the embryo.

The presence of the parasite is not suspected until blocking of some of the lymph-channels gives rise to one of the conditions previously mentioned. The parasite is often abundantly present in the blood of the inhabitants of the tropics and subtropics.

The **filaria medinensis, dracunculus medinensis,** or **guinea-worm,** of which only the female is known, is about 60

cm. to 90 cm. in length and 2 mm. in diameter, and is usually solitary, although not always so. The parasites—probably both male and female—enter with the food; only the female develops. It penetrates the mucosa and eventually reaches the subcutaneous tissues, in which it completes its development. Harrington does not believe in the entrance of the parasite through the alimentary canal. He believes that it is introduced either in some embryonic form, as by the mosquito, or that in some other way it gains access to the subcutaneous tissues directly from without. In no other way can he explain the fact that over seventy-five per cent. of the lesions occur in the lower extremities, and the greater number below the knee. During the period in which the parasite is developing in the subcutaneous tissues it may be distinctly palpable; finally suppuration ensues and the worm is cast off, with innumerable ova, which enter water, where, in the cyclops (?), further development occurs. The parasite has been observed in a patient, a native, and always a resident, of Philadelphia, but it is rare in this country. The suppurative and inflammatory lesions that follow the deposit of the parasite, and that continue during its discharge, form the anatomic basis of the morbid condition called *dracontiasis*.

Among the other filaria occasionally observed in man are: *filaria bronchialis*, found in the bronchi; *filaria loa* (3 cm.), found in the conjunctiva; *filaria hominis oris*, in the mouth; etc.

Our knowledge of the evolution of filaria outside of the body is still incomplete. Exactly what animal constitutes the intermediary host, if such a host is necessary, has not been conclusively established. The present tendency is to believe that some member of the mosquito family may act as intermediary host, either depositing the altered parasite in drinking-water or directly inoculating in a way analogous to that observed in malaria.

Trichocephalus dispar, or **whip-worm**; the female measures about five centimeters; the male is shorter. The anterior two-thirds of the body is thread-like; the remainder is conic, and in the male is rolled like a spring. The eggs are oval, 0.05 mm. long, with thick shell, which, at each end, possesses a knob-like protuberance. The parasite inhabits the colon, particularly the cecum, and may invade the small intestine and the vermiform appendix.

Tapeworms, or Cestodes.—Of these, four only are of sufficient interest to merit description:

1. **Tænia mediocanellata** or **saginata**, or **beef tapeworm.** The head is quadrate, 1.5 mm. to 2.25 mm., surmounted by four suckers arranged in a quadrangular outline, in the center of

which is a fifth rudimentary sucker or flattened groove; the head is void of hooklets, hence the worm is known as the "unarmed tapeworm." The head is attached to a slender neck, varying in length and terminating in the first link, proglottis, zooid, or segment—terms used synonymously. The segments when fully developed are between 8 mm. and 10 mm. broad and about 18 mm. long, and thicker than the proglottides of the tænia solium; like all tapeworms, each segment is hermaphroditic. The genital pores are placed laterally; the uterus shows dichotomous branching more characteristically than the tænia solium; the number of branches varies, but is approximately about fifteen; the

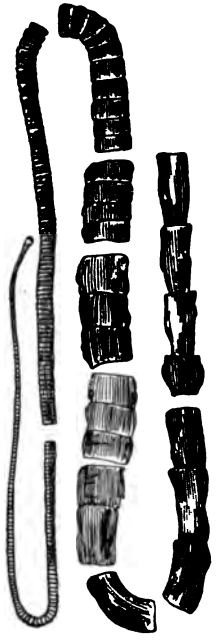


FIG. 158.—TÆNIA SAGINATA.—(*Gould.*)

FIG. 159.—CEPHALIC END OF TÆNIA SAGINATA.
A. Retracted head. B. Extended head.

segments are commonly thrown off spontaneously, while the tænia solium rarely sheds a single proglottis. The length of the worm varies greatly; the number of segments may exceed 1000, and the entire worm may measure between four meters and ten meters. The ova constantly appear in the stools, and the segments show the uterus distended with them. Each ovum is 0.03 mm. in its long axis, is ovoid, or egg-shaped, with a striated outer membrane and a thick shell. The eggs and segments thrown off in the feces are ingested by the ox; the larva or juvenile parasite is liberated, and reaches the muscles,

for the most part, although it has been observed in the heart, lungs, and liver. At the point of deposit there develops a cyst, varying in size from 2 mm. to 2 cm. in diameter, whitish in color, and oval in outline. In this is the larval worm ; the cyst wall is of connective tissue. In this stage the parasite is known as *cysticercus saginata.* Beef rarely contains many such cysts, and their small size not uncommonly causes them to be overlooked. Beef containing the cysts is said to show "measles." It is not known that man suffers from cysticercus saginata.

2. Tænia solium, also known as the **pork tapeworm, solitary tapeworm,** and **armed tapeworm.** The name tænia solium, or solitary tapeworm, is not appropriate, as the pork tapeworm is more commonly multiple than the beef tapeworm ;

FIG. 160.—HEAD OF TÆNIA SOLIUM. ON THE RIGHT, EGG OF TÆNIA SOLIUM.—(*Gould.*)

FIG. 161.—CYSTICERCUS CELLULOSÆ. COMPLETION OF HEAD FORMATION.—(*After Leuckart. — Coplin and Bevan.*) × 12 diameters.

indeed, Leidy regarded the latter as rarely multiple. The adult parasite is a soft, white, band-like worm, rarely over four meters in length. The head is round, 0.5 mm. to 1 mm. in diameter ; there are four discoid or cup-like suckers and a centrally placed papilla, proboscis, snout, or rostellum, surmounted by two rows of hooklets, each row having from twelve to fourteen hooklets ; the hooklets of the inner row are the larger. The neck is very thin, about 2.5 cm. in length, terminating in the gradually developing segment. The segments are from 10 mm. to 12 mm. long, and from 6 to 8 mm. broad. The proglottides differ in this respect from those of the beef tapeworm ; the segments nearer the head may be much broader than long. The uterus is broader, coarser, and the median tube larger, with fewer branches—six to ten, but little over half the number commonly seen in the beef tapeworm. The eggs are about the same size as those of the beef tapeworm, 0.03 mm., but more spheroid.

The **scolex, larval, juvenile,** or **cysticercus form** of the tænia solium has long been known, but Küchenmeister, by feeding experiments, demonstrated that the so-called **cysticercus cellulosæ** is but the larval form of the tænia solium. The larvæ are most frequently developed in the hog, gaining ingress as already described when considering the similar stage in the beef tapeworm. The habits of the hog, however, render measles much more common in that animal than in the ox. Either by the accidental contamination of the hands and subsequent ingestion

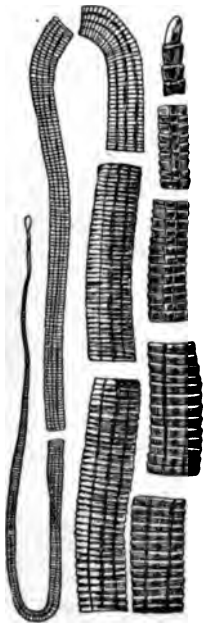


FIG. 162.—BOTHRIOCEPHALUS LATUS.—(*After Leuckart.—Gould.*)

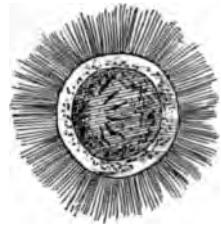


FIG. 163.—FREE-SWIMMING EMBRYO OF THE BOTHRIOCEPHALUS LATUS.—(*After Leuckart.—Gould*)

FIG. 164.—CLUB-SHAPED HEAD OF THE BOTHRIOCEPHALUS LATUS.—(*After Leuckart.—Gould.*)
A. Seen from the edge. B. Seen from flat surface.

of the ova, or possibly by regurgitation during vomiting, occasionally the ova reach the human stomach; as in the beef larvæ in the ox, the liberated larvæ of the solium in man may become widely disseminated. Cysticercosis in the insane is usually the result of coprophagy. When the parasite lodges, a cyst follows, and whether in man or the hog, a "measle" results. The cyst formed is much larger, as a rule, than in the ox, and may attain the size of 20 mm., the beef measle rarely exceeding 7 mm. While the beef measle is unknown in man, this form is not infrequent.

The method of invasion is probably the same from both cysticerci; both the embryos, when liberated in the stomach, have six hooklets, arranged in pairs, by which they tear and propel their passage through the wall of the stomach or intestine.

3. **Tænia lata, broad tapeworm,** or, more correctly named, as it belongs to another genus, **bothriocephalus latus.** The head is clavate, rather elongated, has a long elliptic sucker on each side, measures about 1.5 mm. long by 1 mm. wide, and is without either rostellum or hooklets. The fully developed joints are from two to four times as broad as long; the breadth of the link may reach 1.8 cm. The genital aperture is always on the one side, the ventral aspect, and is central. The eggs are brownish, oval, 0.07 mm. in length, and the shell is furnished with a lid or operculum,

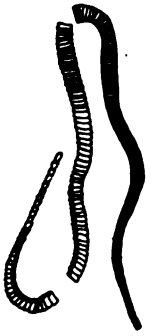


FIG. 165.—TÆNIA FLAVOPUNCTATA.

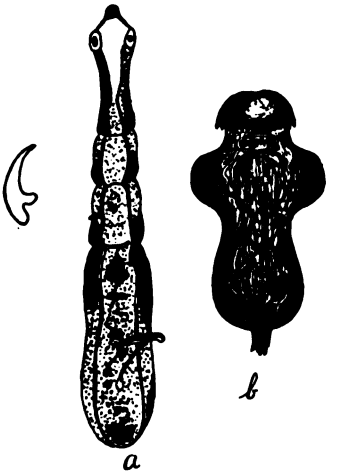


FIG. 166.—TÆNIA ECHINOCOCCUS.—(*After Leuckart.—Coplin and Bevan.*)

a. Adult parasite. *b*. Head of echinococcus veterinorum. On the left, a detached hooklet, as seen in fluid from cyst.

through which the embryo escapes after some months in water. Braun has observed scolices, believed to be of the bothriocephalus, in pike and trout, and by feeding the fish to dogs has led to the development of the tapeworm in the dog. The fully developed worm is said to be the longest of tapeworms.

4. **Tænia flavopunctata** is a short tapeworm, not exceeding 40 cm. in length. The segments vary in length from 0.2 mm. at the neck to 0.5 mm. when fully developed, and in breadth from 0.6 mm. to 2.5 mm. at the same points. A peculiarity of the segments is the alternation of fertile with sterile segments, the former so laden with eggs as to obscure its interior and being

much larger than the nonova-bearing links. The eggs are spheroid, brownish in color, with a diameter of 0.07 mm. Nothing is known of the larval stage of the parasite.

Tænia Echinococcus, or Dog Tapeworm.—The sexually mature worm inhabits the intestine of the dog and wolf. It is an insignificant parasite in appearance when compared with the larger forms, rarely attaining a length of five millimeters. When fully developed, there are five segments; the anterior is slender and is continuous with the head; the following segment is the

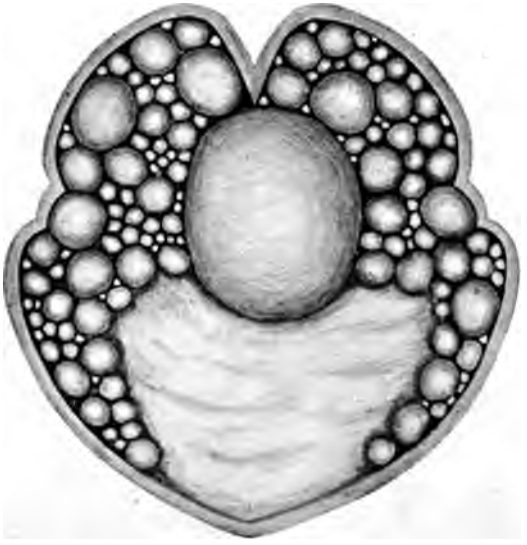


FIG. 167.—HYDATID CYST, SHOWING DAUGHTER CYSTS.

In the lower part of the figure is a whitish mass containing parts of the walls of ruptured daughter cysts. The thick wall of the mother cyst is well shown. (Removed by Dr. H. R. Loux from the liver of a man aged twenty-seven years. The illustration is two-thirds the natural size. Weight, 197 gm. The patient recovered.)

shortest, and the last, the longest. Often more than half of the length of the parasite is in the last segment; from time to time the large link is thrown off, so that it is not uncommon to find but the three proglottides. The parasite is short lived, and is probably the least prolific of the tapeworms; this is compensated for by the proliferative power of the parasite in the juvenile or larval stage. The anterior segment, or scolex, is surmounted by four suctorial discs, anterior to which, between the quadrately placed sucking discs, is the rostellum, with its hooklets, numbering from thirty to forty. The adult parasite is not found in man. The

ova thrown off by the parasite, entering the alimentary canal of man and some lower animals, hatch the embryo, which, wandering into the tissues of an organ, develops into a cyst—the encysted parasite. These cysts occur in three forms:

1. **Echinococcus scoliciparіens, echinococcus granulosus,** or **echinococcus veterinorum,** is a bladder-like cyst, varying in size, often 5 cm. to 15 cm., or even 20 cm., in diameter. The wall of the cyst is formed of two layers, as a rule, easily distinguished from adjacent structures and from each other. The outer layer is supplied by the invaded organ, and is called the cuticular membrane, the tissue of which shows distinct lamination; the inner layer, which is finely granular, constitutes the

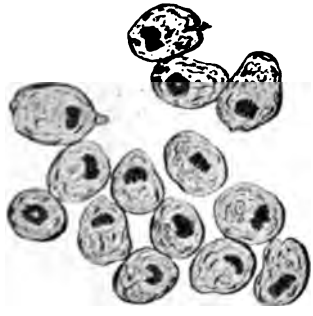


FIG. 168.—ECHINOCOCCUS. A GROUP OF SCOLICES.—(*From Dr. Loux's case,* see Fig. 167. ⅙-in. obj.; 1-in. oc.)

a

FIG. 169.—ECHINOCOCCUS.
Scolex: *a*, pedicle of attachment to endocyst. Just above are shown the somewhat disarranged hooklets.—(*From Dr. Loux's case,* see Fig. 167. ¼-in. obj.; ⅙-in. oc.)

granular or parenchyma layer. When the cyst has attained a diameter of 2 cm. to 10 cm., the development of brood capsules begins. These will be found attached to the granular layer, first as dot-like bodies, later as distinct cysts, in which many young parasites occur; hence they are spoken of as brood cysts. The heads or scolices projecting into the cyst are about 0.3 mm. long, have developed four suckers, and a rostellum with attached hooklets; the interior shows a vascular system and sometimes granular, chalk-like bodies within; at times a parasite may be found with the scolex invaginated into the posterior part of the body, as though retracted.

2. **Echinococcus hydatidosus, echinococcus altriciparіens,** or **echinococcus hominis,** is characterized by the development

of daughter cysts, probably from degeneration of the brood capsules already described. From the daughter cysts another generation of parasites may develop, forming still another series of cysts. The number of daughter cysts may be enormous: as given by Thoma, 1000.

3. Echinococcus multilocularis bears little resemblance to the forms just mentioned; the cysts never attain any great size, but occur in enormous numbers. The liver is the common site of this form, which is very rare in the other organs. Earlier observers regarded the growth as an alveolar, colloid tumor. The cysts rarely attain a diameter of over one centimeter, are spheric or ovoid, the wall formed by a dense connective-tissue membrane, which, under the microscope, may contain still smaller alveoli; the alveoli are filled with a more or less gelatinoid or colloid material containing a few of the histologic elements of the scolex. Often only on prolonged examination can these be demonstrated. The cysts may communicate with one another.

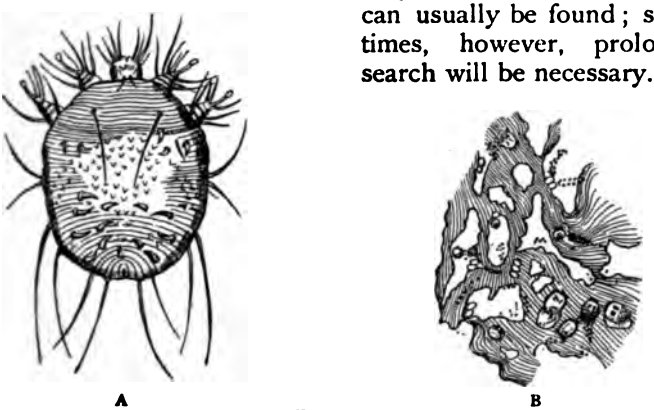
FIG. 170.—ECHINOCOCCUS-HOOKLETS.—(*From Dr. Loux's case*, see Fig. 167. ¼-in. obj.; 1-in. oc.)

Site.—Echinococci may occur almost anywhere, but over forty-five per cent. of the cysts are found in the liver. (See Parasitic Cysts.)

Demonstration.—The diagnosis of echinococcus-cyst is commonly based upon the finding of the hooklets or scolices. The presence of a fluid with a comparatively low specific gravity, and nonalbuminous or containing but a minute trace of albumin, should always be looked upon as indicating an echinococcus-collection. When the fluid is clear and contains but a small quantity of suspended material, sedimentation should be permitted to take place, and the sediment may be further brought together by the centrifuge, if necessary. A small quantity of the sediment is placed on a slide in the same manner as already directed for urine; examination made by the ¼-inch objective will usually show the hooklets quite plainly. Occasionally, coccidial cysts, and possibly cysts arising from other causes, contain sickle-shaped bodies, which may mislead the inexperienced. The hooklets of the echinococcus have on the concave side a knob, or protuberance, or hump, which never has been successfully imitated by anything with which the author is familiar. The brood capsules and contained scolices can rarely be demonstrated in the fluid drawn from such cysts by tapping. If, however, the cyst wall be accessible, gentle scraping will usually detach the cap-

sules, some of which may escape rupturing. These are best shown on the slide under comparatively low magnification—1-inch or ½-inch objective. (See Figs. 168 and 169.)

Occasionally, the cyst may be inspissated as a result of the death of the contained parasites. Under such circumstances the contents may be cheesy, resembling the caseous collections of tuberculosis and syphilis. The demonstration of the hooklets in this material becomes somewhat more difficult. A considerable quantity of the suspected material should be washed in alcohol, the alcohol drained off, and the washing repeated; this may be followed by washing in ether to remove any fat, and, finally, the remaining sediment may be removed to the slide and examined as already directed. If these directions are carefully followed, the hooklets can usually be found; sometimes, however, prolonged search will be necessary.



A B

FIG. 171.

A. Acarus scabiei. B. Portion of epidermis, showing the burrows with their contained eggs. —(*After Leuckart.—Gould.*)

Acarus scabiei (arachnida), the parasite that causes scabies or itch, is known as the **itch-mite** or **sarcoptes hominis.** The female is nearly double the size of the male, and can often be picked out of the furrows found in the skin in cases of itch. The parasite is from 2 mm. to 5 mm. in length, and over one-half as broad. It possesses four pairs of legs, two pairs anteriorly and two posteriorly. From each of the foremost pair of the anterior legs extend delicate processes, supplied at the distal end with discoid terminations for attaching themselves to surfaces; in the male these addenda are on the hindermost pair. The other legs end in bristles. The posterior border has a number of bristle-like hairs; similar hairs are seen on the rounded head of the mite.

The parasite burrows into the epidermis, in which it forms

cavernous systems attended with inflammation of the adjacent mucous layer. In the cuticular caverns the female deposits her eggs, which hatch into young mites. These burrow, shed their external coatings, and repeat the process of reproduction of kind.

Leptus autumnalis, or *harvest-mite* (larva of trombidæ), is a red-colored parasite deposited upon the skin from grass, bushes, and certain cereals; it induces inflammation by its bite or by boring into the epidermis.

Pentastoma denticulatum is the juvenile form of the pentastoma tænioides. The mature female is 50 mm. to 125 mm. in length and 6 mm. to 10 mm. broad; the male is much smaller—15 mm. to 25 mm. long and 2 mm. to 5 mm. in breadth. The larva is between 3 mm. and 5 mm. in length, and is from 1 mm. to 2 mm. wide—an egg-shaped mass occasionally found in the viscera. The mature worm is found in the frontal, nasal, and maxillary sinuses of some of the domestic animals.

The **demodex,** or **acarus folliculorum hominis,** inhabits the ducts of sebaceous glands and occasionally the hair follicles. It is broad just back of the head, from which point it tapers down to a blunt hinder extremity; at the broadest part are four short, thick legs. The length of the parasite varies greatly,—between 0.5 mm. and 1 mm.,—and the insect is usually about one-tenth as broad at the widest point.

Ixodes ricinus, or *wood-tick*, inhabits decaying wood in dry places (dry rot of timber), from which it attaches itself to dogs, and occasionally to man. The head is black or brownish, and supplied with a boring disc, which penetrates the skin, and through which the parasite sucks blood.

Pediculus capitis, pediculus ordinarius, *head-louse*, or *common louse*, inhabits the hairy scalp. The adult parasite is about 2 mm. to 3 mm. in length, and, pathologically, is an epizoon, securing nourishment by attacks upon the skin. The irritation produced by the bites is sometimes followed by inflammation, which may be eczematous in character. The eggs are oval, with slightly flattened ends, attached to the hair by a chitinous cement, which also covers them. An egg hatches out in from seven to ten days.

Pediculus vestimenti, pediculus corporis humanus, *clothes-louse* or *body-louse*, inhabits the clothing, in which it deposits its eggs. The fully developed parasite is considerably larger than the head-louse. From the clothing the parasite makes incursions to the skin, from which it obtains nourishment. The bites induce changes similar to those of the head-louse.

Pediculus pubis, pediculus inguinalis, phthirius pubis or **inguinalis,** or *crab-louse*, infests the hairy pubis, axilla, and, rarely, the beard and eyebrows. The parasite is smaller than either the head- or body-louse. Its habits are practically the same as those of the head-louse.

FIG. 172.—PEDICULUS PUBIS.

Cimex lectularia, cimex hirundinis, or *bedbug*, dwells in beds, floors, and cracks of woodwork, from which it invades the skin, the bites producing slight inflammatory lesions. The adult parasite is 3 mm. to 6 mm. in length; the eggs are laid between the months of April and October, and require eleven weeks to hatch and develop the mature parasite.

Pulex irritans, pulex hominis, or *human flea;* the **pulex serraticeps, pulex felis, pulex canis,** or *dog flea.* The two parasites closely resemble each other, and by some are held to be identical. They infest the hair of the dog and cat, from these animals wandering to man. Closely related to these is the *sand-flea*, **pulex minimus cutem penetrans,** or **pulex penetrans,** an excessively annoying parasite, smaller than either of the foregoing, and found in the sandy areas of the tropics and subtropics.

The **mosquito** and certain forms of the *gnat* belong to a subdivision of the parasitic genera known as the *culex.* The *culex ciliatus*, or *large mosquito;* the *culex equinus*, or *horse mosquito;* the *culex damnosus*, or *common mosquito* of the lowlands of the Eastern States, and the *culex pipiens* of Europe, are the most important members of the culex group. The local lesions induced by these parasites, while not wholly unimportant, are now considered of more importance than formerly. It is held by Manson and others that these parasites are intermediate hosts for the smaller parasites, the larva of the filaria, and that certain mosquitos inoculate man with the parasite of malaria.

Maggots, occasionally seen in dead tissues, and, before the antiseptic methods of to-day, one of the parasites found in wounds, are the larval form of certain flies. The eggs deposited on the wound surface, dressings, etc., hatched, the resulting juvenile parasite being known as a *maggot.*

Hematozoon, or **hematomonas malariæ,** also known as the **plasmodium malariæ.** During the period in which the temperature of the malarial patient is rising and approaching the chill

stage, and in many cases quite independent of the paroxysm, if a drop of blood be prepared for examination as directed (see Technic of Blood Examination, chap. I, part III), the parasite will commonly be readily found. Presuming that the examination be begun at the period when the chill is in progress or impending, in the tertian intermittent form of malaria: The parasite is now in the sporulation stage, a period in the cycle of its development when not of easy demonstration. A magnification of about 1000 diameters ($\frac{1}{12}$-inch oil immersion) will be found convenient, but not absolutely necessary, as the discoverer of the parasite, Laveran, commended a magnification of 600 diameters ($\frac{1}{6}$-inch or $\frac{1}{8}$-inch objective, with a good eyepiece). Carefully focusing on a part of the field in which the red blood-cells are thinly spread, the slide is slowly moved, a close watch being kept for pale bodies in the corpuscles or for pale corpuscles, in which the parasite is to be looked for. At times a red cell will be found, with a mulberry-like mass occupying the greater part of the cell; the cell is likely to be deformed, ovoid in outline, with loss of evident biconcavity. (See Fig. 173, A_1, A_2, A_3, A_4.) A little later the red blood-cell breaks up and the **sporulating plasmodium** is freed in the blood. Its recognition in this stage is most difficult; the somewhat irregular hyaline bodies are not readily recognizable until they again attach themselves to a red blood-cell. Shortly after the paroxysm red blood-cells appear with the so-called **epicorpuscular forms,** the hyaline ameboid bodies usually eccentrically placed, almost never round, but irregular, with out-branching, pseudopod-like arms, and, if the slide is warm or the observation made in a warm room, the hyaline body changes its shape and position. It is owing to this ameba-like motion that we can most readily detect its presence. The so-called vacuoles or hydropic spots occasionally seen in the blood may mislead the inexperienced and unwary; the knowledge of their possible presence should prevent such an error. As soon as the parasite becomes fully **intracorpuscular** and advances in its growth, there appears agmination of the red blood-cell coloring-matter apparently into the parasite, which, therewith, assumes the **pigment stage**; now it is most easily recognized; it occupies a variable extent of the blood-cell, and has within it the moving granules of pigment; if the cell be cooled or in the least dried, pigment motion ceases, and the quiet pigment closely resembles extraneous material that microscopists roughly designate as dirt. The freshly drawn blood with the moving pigment within the parasite, and the latter again within the red cell, offer no excuse for failure in identification.

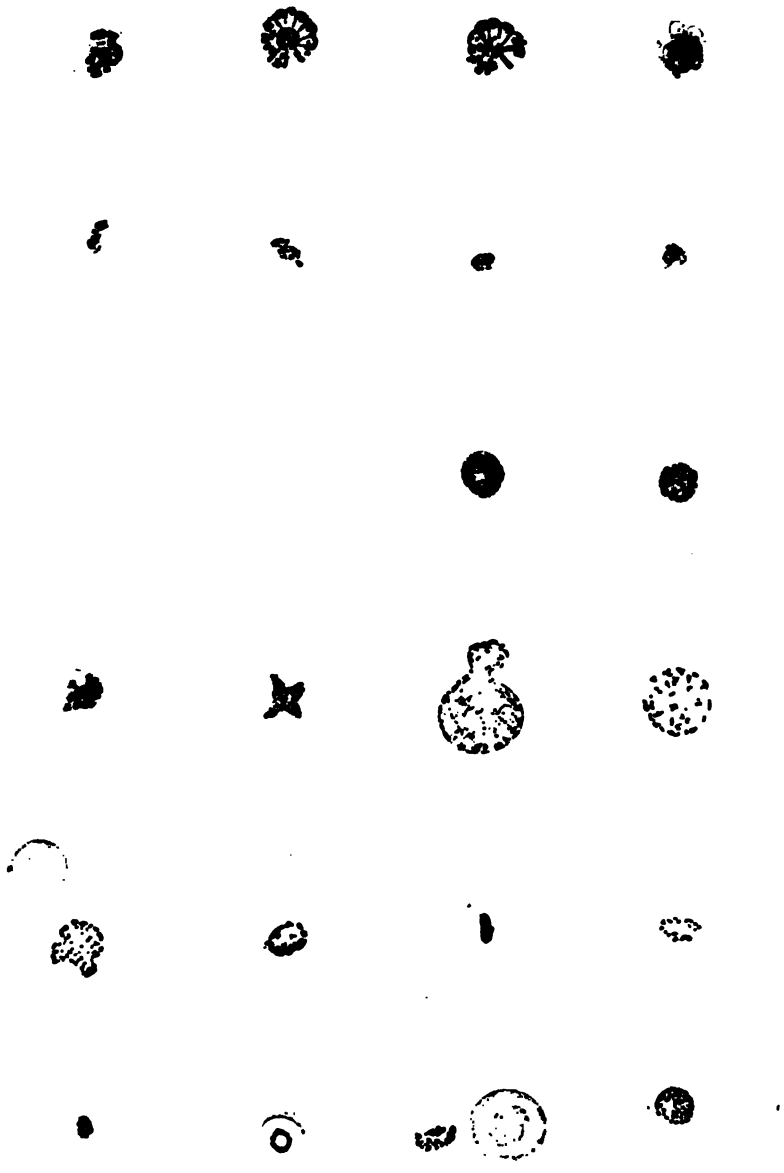


FIG. 173.—ILLUSTRATING DIFFERENT FORMS OF THE MALARIAL ORGANISMS WITH THEIR STAGES OF DEVELOPMENT.—(*Tyson's "Practice of Medicine."*)

A_1, A_2, A_3, A_4. Sporulation stage. B_1, B_2. Sporules separating. A_1, A_2, A_3, A_4, B_1, and B_2. Stages in the so-called rosette form of the parasite. C_1, C_2. Free sporules. D_1, D_2. Epicorpuscular forms. Nonpigmented, or hyaline, ameboid bodies. E_1, E_2, E_3, E_4. Intracorpuscular forms, with varying amounts of pigment. F_1, F_2. The large extracorpuscular body. G_1, G_2. The flagellate forms. $H_1, H_2, H_3, H_4, H_5, H_6$. The parasite of estivo-autumnal malaria. H_1, Crescent showing remains of red blood-cell in the concavity. H_2, H_3, H_4, and H_5. Ovoid and discoid or ring forms of the parasite. H_6. Flagellated organism.

(See Fig. 173, D_1, D_2, E_1, E_2, E_3, and E_4, partly diagrammatic representations of the nonpigmented and pigmented parasites.) The number of parasites in any specimen of blood varies, but in a fairly marked case one should expect at least one to every two or three fields, but a more extended search may be necessary.

As the development of the parasite progresses, faint lines radiate from the center toward the periphery, near which each pair of marginal markings are joined by a short arc; near the outer extremity of each of these wedge-shaped masses we see a small granular body, possibly the nucleus. The clumps of these wedge-shaped masses around a common center give the parasite a **rosette** shape. This rosette may or may not be surrounded by a visible rim of the remaining red corpuscle. This is the mulberry-like form, which is the sporulating stage, ready to free the spores, at which time the malarial paroxysm usually occurs. The freed sporules are not recognizable in the peripheral blood, but probably are liberated in the large viscera, in which they attach themselves to the red corpuscles and again appear in the peripheral circulation.

The differentiation between the tertian and quartan parasites is based upon certain differences in the morphology at various stages in their development:

	TERTIAN PARASITE.	QUARTAN PARASITE.
Size, ...	About that of red blood-cell.	Smaller.
Pigment, ...	Fine, light, active.	Coarse, dark, less active than tertian.
Red blood-corpuscle, . .	Swells and fades in color.	Shrinks around the parasite and deepens in color.
Sporulation segments, . .	Fifteen to twenty or more.	Usually not over ten, at times fewer.
Cycle, ...	Completed every other day.	Completed every third day.

The parasite of irregular malarial fever—the *estivo-autumnal type*—is less regular, so far as we can ascertain, in the cycle of its development, but presents certain characteristics by which its identification is assured. In the earlier stages it may escape notice, as it is not abundant in the peripheral circulation. The small *hyaline bodies* are few, very small, ring-like or crescentic, with scant pigmentation; the red cell containing the parasite is com-

monly much shrunken, the hemoglobin, with but little granulation, surrounding the parasite, leaving the outlying segment of the red blood-cell but faintly, if at all, colored. The parasite in this stage is small, rarely occupying as much as one-fourth of the cell. The later stage of the cycle occurs in the viscera. Later there appears the **crescentic form,** upon the recognition of which the diagnosis so largely depends. (Fig. 173, H_1, H_2.) Crescents are not seen until the fever persists several days. They are assumed to develop from the hyaline form, which gradually enlarges, loses its motility, and becomes crescentic, with agmination of its pigment granules near its center. Crescents occur in freshly drawn blood, and, when observed under suitable conditions, may be seen to assume elliptic, ovoid, and round forms (Fig. 173, H_3, H_4, H_5); when the round form is attained, the pigment granules become actively motile, which may be a step toward sporulation.

Extracorpuscular and **flagellate forms** of the malarial parasite are seen as changes not presumed to occur in the circulating peripheral blood. The former are believed to be the same as the intracorpuscular bodies liberated from the blood-cell by post-mortem changes, and not observed until some moments after the blood is drawn. At times, particularly if the blood drawn be kept in a moist chamber and warmed to near the normal blood-heat, there appears a series of phenomena, by close attention to which flagella may be demonstrated. First, around or near a malarial parasite may be seen a group of red corpuscles in active motion, as though being lashed about; by careful focusing we may make out a filmy, almost imperceptible, whip-like process, attached to the malarial parasite and in active motion; it may show a few pigment granules along its length, and possibly at its end a slight bulbous enlargement, in which there may be pigment. (Fig. 173, G_1, G_2, and H_6.) Occasionally a flagellum may become detached and show active motility, progressing among the corpuscles through several fields.

The foregoing brief description applies to the fresh slide of blood. When, for any reason, staining is found necessary, the methods advised in the section on the blood may be utilized. (See The Blood, chap. I, part III.)

Many views have been maintained as to the route by which the malaria organism finds access to the blood. It has been held that introduction into the circulation occurs through air, water, food, etc. At present the trend of scientific opinion is toward the view that infection occurs through the bites of certain insects. It is now generally conceded that the most important

infecting parasites are the anopheles maculipennis and the culex pipiens.* The mosquito takes in the malaria organism with the blood, and within the body or glands of the mosquito it is not improbable that certain changes take place in the malaria parasite; in other words, the mosquito acts as an intermediary host, within which the malaria parasite undergoes alterations in form, and possibly in some of its essential powers of infection. Sporule forms of the parasite have been found in the venomosalivary gland, and as the lancet of the mosquito is anointed by the secretion from this gland, it becomes possible to understand how infection may be brought about.

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*Koch, "Deutsch. med. Woch.," Sept. 14, 1899.

CHAPTER II.

HYPERTROPHY, HYPERPLASIA, METAPLASIA, HETEROPLASIA, ATROPHY, HYPOPLASIA, AGENESIS OR APLASIA.

Hypertrophy may be defined as increased functional power having a tendency to persist, and that is beyond the normal for a given tissue under its existing conditions; thus, a heart weighing twelve ounces may be normal for the adult, but would be hypertrophic in a child. Hypertrophy is not simply increased size: *e. g.*, the amyloid liver may weigh six kilos and be functionally inactive. The foregoing definition also excludes tumors, which perform no function. Hypertrophy is usually associated with abnormal size and weight, but the reverse is not necessarily true. Many clinicians and pathologists teach that hypertrophy is essentially a structural alteration; in other words, that it is simply an increase in all the elements entering into the formation of an organ or tissue, each element retaining its normal relation to the associated structures. It is to be granted that this is true, but a definition, or even the idea of hypertrophy, based simply upon this fact alone, must of necessity be erroneous. Occasionally, one finds a tumor of the mammary gland that structurally can not be differentiated from the normal gland. The glandular elements are exactly like those normally present, but the mass is surrounded by a capsule and is sharply differentiated from the normal gland. The normal gland being called upon for the manifestation of its associated functions, will hypertrophy, while the tumor mass may or may not show any such enlargement. It certainly produces no milk, nor are its false ducts and imitative acini connected with the normal structures. It is a new growth—something situated in the mammary gland, but having no more connection with the functions of that structure than if it were located elsewhere in the economy. The continued power to do more work than normal implies, and is nearly always associated with, an increase of the tissue performing the function; but this does not alter the fact that the essential feature of hypertrophy is power to accomplish more work than the normal organ. Hypertrophy must be differentiated from

the so-called **reserve force of organs**; thus, the heart, during a period of intense excitement, may perform effectually two or three times the work that is normal for it, and still the organ may not be hypertrophied. The condition, however, does not persist; it is temporary.

Causes of Hypertrophy.—Increased work with supplied nutrition are the causes most active in extra-uterine life. Examples of increased work with supplied nutrition, followed by hypertrophy, are abundant. The most familiar instance, and the one most often cited, is the hypertrophy of the heart that occurs as a result of alterations of the valves or orifices, thereby increasing the force demanded of the diseased organ. Thus, a narrowed aorta or aortic orifice may demand twice the normal force to propel the blood through the abnormal obstruction. As an admirable example of increased functional power, the properly trained athlete may be cited. Evidence is not wanting to show that, under careful and continuous training, nearly all the tissues of the body may take on additional activity. These, however, fail to account for certain enormous overgrowths of organs or tissues that occasionally occur. Thus, general or partial **giant growth** may arise without any apparent extra demand for work, although, of course, the extra nutrition is supplied. This phenomenon (giant growth) has been said to arise from **congenital impulse**—an expression that only moves our ignorance of the actual cause back to a period in which we know less of the functions of organs. Since we have come to appreciate the fact that many organs perform functions of nutrition, secretion, heat production, etc., it is to be conceived that some extraordinary call has been made upon them, the nature of which we can not in the present state of our knowledge estimate; this extra call may constitute the demand for additional tissue, and hence hypertrophy. There can be no apparent reason for an enormous hypertrophy of the facial and long bones, as is sometimes seen; but there must be some reason for the change, and whether this be attributed to changes in innervation or to unusual demand for some functional activity that we can not estimate (such as blood-making by the marrow) remains to be further studied. The two conditions—supplied nutrition and conversion of the added nutrition—are necessary; if work be increased without sufficient nutrition, wasting occurs; on the other hand, nutrition may be abundant and, without work, the tissue may waste; as an example of the latter, we have the wasting of the muscles of the arm when splinted for the treatment of fracture—the nutrition may be just as abundant as when the organ is uninjured.

Hypertrophy is sometimes said to be true or false; the latter is not possible. The term false hypertrophy, or **pseudohypertrophy,** is applied to large organs in which the increase in size is not attributable to increased functional power or to increase of the elements in the normal proportions, but rather to increase in size due to the invasion of the tissues by a new element, overgrowth of some existing tissue, or some similar condition. The enlargement of the liver, associated with amyloid disease, fatty infiltration, or red atrophy, may be taken as types of so-called pseudohypertrophy. The term is a poor one, and should not be used.

Hypertrophy is said to be **simple** and **numerical**; by the former is meant an increase in the size of the cells, and by the latter, an increase in the number of cells. Kölliker has observed that the unstriped muscle-fiber of the uterus, at the end of gestation, is eleven times the length and four times the width of the normal fiber of the nonpregnant organ. Hare and Coplin, in their studies of the influence of digitalis on the cardiac muscle, note a marked increase in the transverse measurement of the fiber, an observation supported by Tangl, who found that in the ordinary form of hypertrophy of the heart there was an increase in the size of the muscle-fibers, which increase bore a definite relation to the increased weight of the organ. It is probable that in most instances of hypertrophy there is an increase in the number of cells as well as an increase in the size of the existing elements, both old and new; it is not probable, however, that both enlargement and increased number of cells are equally marked in all cases.

Physiologic hypertrophy differs from other forms of hypertrophy in that it anticipates the increased work that may be demanded of the tissue. In a certain sense all forms of hypertrophy are physiologic; hypertrophy is not a disease; but the condition referred to as physiologic hypertrophy is typified in the enlargement of the mammary glands and the increase in muscular power of the uterus in anticipation of lactation and labor. Unlike all other forms of hypertrophy, this condition apparently arises independently of existing increased work; as far as our knowledge goes, it anticipates such work.

Hypertrophy is said to be **compensatory** when one organ performs the work of another; thus, if one kidney be diseased, the opposite organ may undergo hypertrophy; if one lobe of the liver be destroyed by disease, the remaining lobes may increase in size. The term compensatory hypertrophy is also used by clinicians in another sense: *e. g.*, if the orifice of the aorta has been narrowed, thereby demanding more cardiac force, and if the

heart hypertrophies to meet the new condition, it compensates from the abnormal obstruction, and the hypertrophy is said to be compensatory. Once such hypertrophy develops, and later conditions lead to its failure, it is said that the compensation has failed; a like expression is not uncommonly used to indicate a preliminary failure. Compensatory hypertrophy develops with more certainty in the young, while in extreme age the tissues commonly fail to respond to demands made for additional work.

When a tooth has been extracted, the opposing tooth becomes longer, as the result of diminished wear, and possibly of lessened resistance. This is sometimes referred to as a form of hypertrophy.

Limitations of Hypertrophy.—If the occurrence of hypertrophy depended entirely upon the demand for work, there is no reason for its failure to progress indefinitely. Experience, however, shows that a point is always reached, sooner or later, when compensation fails, and work demanded beyond this point leads to wasting. As previously remarked, the older the individual, the earlier this occurs—a fact that suggests that the blood-vessels are responsible, to a certain extent, for the arrest of the process. It is observed in athletes that if a man has thoroughly trained early in life, he remains competent to train into "condition" throughout the major part of his days. Early in life the blood-vessels are more capable of increasing their carrying capacity than in later years—a fact very well known of the arteries; besides, the conditions favoring hypertrophy are more marked in intrauterine life and become less powerful with advancing years. It has been shown that antenatal hypertrophy of the kidney is associated with the formation of new glomeruli and tubules, while postnatal hypertrophy evinces itself only by an increase in the size of the glomeruli and possibly in the length of the tubules.

Theoretically, once an organ begins to hypertrophy there is no reason for arrest of the process, provided the conditions persist; but a stage is eventually reached when the blood supply is no longer competent, the arteries being inadequate or unable to transmit the demanded additional blood. When this stage is reached, not only is hypertrophy arrested, but if the demand for increased work be continued, wasting occurs; clinicians recognize, in the treatment of heart diseases, that, even with well-established hypertrophy and good nutrition, a stage is reached in which the best results are attained by diminishing the work to be done rather than by lashing an already overworked organ and hoping for continued hypertrophy.

Hyperplasia is an increase in the connective tissue of an

organ, either associated with or independent of increase of the elements upon which the functional activity of the organ depends. If there be an increase of the functionally active cells of the organ, the increase in connective tissue must be in excess of that which is normally present, in order to be a hyperplasia. The term hyperplasia is also applied to disproportionate increase in any element of an organ. Thus, a new growth of bile-ducts is spoken of as hyperplasia; newly developed gland-cells, or an excess of one constituent of an organ without corresponding growth of the other elements, is spoken of as hyperplasia.

Metaplasia is the direct transformation of a tissue into a dissimilar tissue. This is only possible of tissues of the same type. Different forms of epithelium may change, one into another, or one connective tissue may be converted into another, as cartilage into bone, or fibrous or loose connective tissue into fat. Transposition of type is not possible; epithelium never becomes connective tissue, nor is connective tissue ever converted into epithelium. An ulcerative process in the trachea, after cicatrization, is covered by flat epithelium from the genetic layers of adjacent columnar epithelium, the process constituting a form of metaplasia. In order that it may be a pure metaplasia there must be no intervention of embryonic tissue. Theoretically, such a thing is possible; but whether a cylindric cell is ever actually converted into a squamous cell, without the intervention of what is essentially an embryonic cell, seems somewhat doubtful.

Heteroplasia implies the production of a tissue in some structure when such a tissue, which may be perfectly normal elsewhere, is not a normal constituent of the organ in question. The development of cartilage or bone in certain glandular structures, such as the parotid, ovary, or testicle, constitutes a heteroplasia. The best type of heteroplastic tissue is a tumor of the typical series. It will be observed that heteroplasia usually implies a change analogous to metaplasia. Thus, in the instances given the bone or cartilage found in the gland must have arisen from connective-tissue elements normally present, and, hence, probably a part of the normal gland. In such elements the proliferative change terminating in the formation of cartilage or bone implies metaplastic power.

Atrophy is the reverse of hypertrophy, and hence is diminished functional power, which has a tendency to persist or to increase, and which is associated with structural alterations in the tissue involved. It is not merely diminished size or weight, as, in the condition known as red atrophy of the liver, the organ may be much increased in size. Atrophy is not an arrest of de-

velopment. Atrophy occurs in developed tissue, although the arrest in development may be followed by atrophy of that tissue that has already developed.

Causes.—Atrophy may be *physiologic: e. g.*, the atrophy of the thymus gland shortly after birth, atrophy of the uterus after labor, atrophy of the sexual organs after the menopause. Atrophy may be caused by *pressure*, as the pressure atrophies of the liver. As a result of pressure from a belt or a corset, a deep fissure may be produced in the liver tissue. Again, atrophy of the hepatic structures may follow pressure brought about in other ways: for example, in red atrophy of the liver the blood dammed back, as a result of obstruction to its onward flow in the heart or lungs, gradually distends the hepatic capillaries, thereby making pressure upon the surrounding cells, which, in turn, is followed by atrophy. (See Red Atrophy of the Liver.) In the chronic indurative processes taking place in the liver the newly formed fibrous tissue, by contraction, presses upon the hepatic lobule and gives rise to atrophy. (See Atrophic Cirrhosis of the Liver.) Atrophy due to pressure is further shown in the absorption of tissues as a result of the constant pressure of an enlarging aneurysm. *Disuse* of a tissue will lead to its gradual atrophy. Atrophy from disuse may be dependent upon lessened nutrition, as it is well known that the inactive tissues may be poorly nourished. This is the type of atrophy that leads in generations to the disappearance of tissues and organs no longer used. The wasting incident to the fixation of a limb in the treatment of fracture is in part due to its disuse, and also, in many cases, the pressure of dressings. *Inanition* or faulty nutrition, whether general or local, will give rise to atrophy; as examples of general atrophy due to inanition we have the progressive muscular wasting that occurs in consumption, in the cachexia of malignant tumors, and in profound blood dyscrasias.

In the atrophies due to faulty nutrition the cellular elements having the most work to do usually suffer most. That this is not always the case, however, is shown by the extreme muscular wasting that occurs in pulmonary tuberculosis, and by the fact that the kidney and liver may not, at the same time, show any perceptible lessening in weight or in functional power.

The lessened nutrition, upon which inanition atrophy depends, must not be too suddenly applied, nor must the starvation of the tissue be extreme; as a result of either of these conditions the tissue may undergo necrosis rather than atrophy. The induction of local atrophy by a local starvation has been utilized in treat-

ment; rapidly growing, inoperable tumors have had their growth successfully limited—for the time being, at least—by ligation of the arteries supplying them with nutrition.

Certain atrophies are spoken of as *trophic: e. g.*, atrophy associated with disease of the anterior cornu of the spinal cord; unilateral neuropathic atrophy of the face. It is presumed that certain elements in the central nervous system preside over nutrition, and that disease or injury of these elements will bring about nutritive changes in the tissues over which they preside; thus, destruction of the motor cells in the cord is associated with wasting of the muscles with which the cells are connected. It is evident, of course, that here we have to deal with a complex process; in addition to the so-called trophic influence of the cells we have the wasting incident to disuse of the muscles involved. *Inflammatory processes* may lead to atrophy by pressure and by interference with the nutrition. It is believed by some that certain substances in the general circulation may manifest a selective activity upon given tissues, thereby leading to their atrophy and absorption. Exactly how this change is brought about it is quite impossible to say, but there can be no doubt that examples apparently coming under this head occur. Atrophy of the thyroid gland during the administration of iodin and atrophy of the extensor muscles of the forearm in chronic lead-poisoning may be cited as examples of atrophic processes apparently depending upon bodies introduced into the circulation by internal administration.

In the cells and tissues involved in atrophy there is general shrinking of the diseased structures; the cells become granular and not uncommonly pigmented; it is reasonable to suppose that in this granular or fatty condition absorption of the cells is readily possible; certainly, functional activity is enormously diminished, if not, in advanced cases, suspended.

This association of structural change with absorption and disappearance of cells has led to the name **degeneration atrophy.** It is probable that all atrophies are associated with some degenerative phenomena in the cells; by no other means can we explain the disappearance of structure. It is held, however, that atrophy is possible without appreciable cell change; such a condition has been termed **simple atrophy.** Again, the term simple atrophy is used to indicate a diminution in the size of the cells, while numerical atrophy implies a reduction in the number of cells. It is possible that in nearly all atrophic processes reduction both in size and number occurs. When the atrophic phenomena are due to the inability of the cell to assimilate supplied

nutrition, the lesion is said to be an **active atrophy**; when the fault lies in deficient nutrition, it is called **passive.** The same causes acting upon different tissues may give rise to atrophy in some and not in others. Again, two tissues, apparently similarly placed with regard to nutrition, may show different degrees of atrophy, although the indications are that the cause acts equally upon the two elements; thus, the connective tissue of glands atrophies slowly, while the parenchymatous structure may show a far more marked atrophic change.

Hypoplasia differs from atrophy in that development has been arrested either before or after birth; it is not the wasting of tissue, but the failure to reach the normal development. The process may involve the whole body, or it may be restricted to one or more organs or parts of organs, or to the organs belonging to a single system; as, for example, hypoplasia of the genital apparatus. Dwarfs are examples of hypoplasia. When the process is not universal, but is restricted to one side of the body or of an organ, as the brain (microcephalus), it is known as **asymmetric hypoplasia.** The cause may lie in incomplete development, or partial occlusion, of the blood supply to the tissues involved. This not rarely proves to be the case where syphilitic endarteritis has lessened the blood supply to an organ or a part of an organ; an example of the first is sometimes seen in the kidney, and of the latter, in the liver. The environment of organs may lead to hypoplasia, as when bands of inflammatory tissue restrict their growth, or failure in the development of the skull limits the increase in the size of the brain.

Agenesia, agenesis, or **aplasia** should be restricted to mean entire failure of development: that there has been no effort at the production of an organ or tissue. This is seen in the kidney at times, and is usually due to obliterative disease of the renal artery. The term is also applied to the disappearance of partly developed organs. It may be used to indicate the failure of a given structure of an organ to develop. As an example of the latter, occasionally the fibrous tissue of an organ develops without any corresponding development of the parenchyma, in which case there is said to be agenesis of the parenchyma.

CHAPTER III.

INFILTRATION AND DEGENERATION.

(A) INFILTRATION.

Infiltration is the "filtering in," or deposition in organs, or the addition to organs, of elements not normally present, or an excess in quantity of a material that is normally present. It will be observed that the term "infiltration" is here applied to a material and not to a tissue, although one must confess that the difference is not striking. If tissues are included as infiltrating bodies, then a tumor invading an organ would be an infiltration; such is not the meaning of the term in the sense here used. The materials studied in the infiltrations are chemic bodies, rather than bodies with definite histologic structure. Thus, fat, lime salts, the various pigments, glycogen, and even amyloid material, are bodies with definite chemic composition, and not composite mixtures of many agents, as are the tissues. It is true that amyloid material has a rather characteristic histologic structure and stain reaction; so have many crystals, but this does not make them tissues, in the common acceptation of the term. Infiltrations are (1) fatty; (2) amyloid or albuminoid or, possibly more correctly, lardaceous; (3) pigmentary; (4) calcareous; (5) glycogenic.

1. **Fatty infiltration** consists in the addition of fat to an organ in which fat is not normally present, or the addition of a large amount of fat in an organ that normally contains less. Under certain conditions the deposit of fat may properly be considered as physiologic. This same deposit, however, carried to excess, may interfere with the nutrition and function of the tissues involved or of adjacent tissues, and when this stage is reached, the process becomes essentially pathologic. As evidence of the physiologic deposit of fat one need but cite the fat normally present in the hepatic cell, which is apparently necessary for the proper functions of that structure. A certain amount of fat is normally present in the subcutaneous tissue, in the orbit, in the perirenal tissues, and elsewhere. Physiologically, the fat deposited in the areas named may perform a number of functions: the first, and probably the most important, function is the

storage of reserve food that may be called upon when the usual source of nutrition for any reason becomes inadequate. The fat in the orbit as well as that around the kidney acts as a cushion, offering to the adjacent organ a certain amount of protection from injury.

Causes.—Increased nutrition ; decreased work ; slowed circulation ; reduced or faulty oxidation. In the increased nutrition fat is stored in the cells, being in excess of the quantity that the cells can utilize for existing demands. If the functional activity of the cell be reduced by lessened demand, and the normal amount of blood is sent to the cell, the nutrition is in excess, and fatty infiltration may result. Moderate slowing of the circulation gives rise to fatty infiltration ; thus, slowing of the circulation

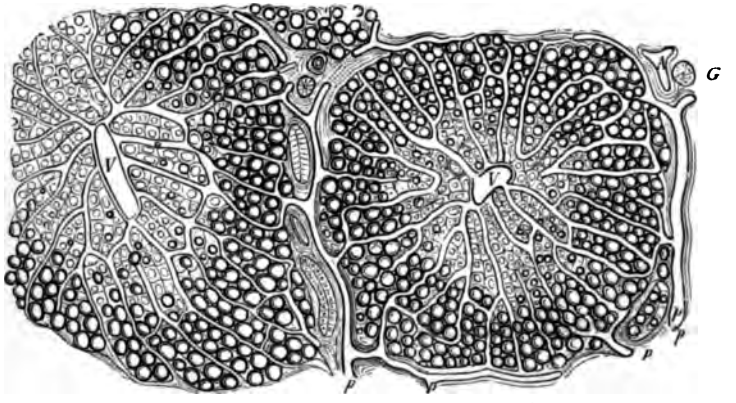

FIG. 174.—FATTY INFILTRATION OF THE LIVER. (Semidiagrammatic.)
V, V. Hepatic vein. *p, p, p, p, p, p.* Portal vein. *A.* Hepatic artery. *G.* Bile-duct. The globular cells loaded with fat are seen in the periphery of each lobule.—(*Rindfleisch.*)

partly accounts for the fat infiltrated into the connective tissue of the omentum and mesentery in cirrhosis of the liver, and also for the fatty infiltration that occurs in the liver lobules in cirrhosis.

The infiltration of fat occasionally seen in the liver in tuberculosis, and associated with marked emaciation, and the infiltration seen in the subcutaneous tissues in chlorosis, where the blood findings would certainly indicate that nutrition is not in an ideal condition, are taken to be examples of fatty infiltration depending upon faulty oxidation. The origin of the stored fat has been a matter of much discussion. It is now generally conceded that it may arise from a number of sources. In the fatty deposits of hypernutrition it is usually held that it represents the fats and sugars in the food, and, to a limited extent, the albuminoids. In

deposits from other sources it is not improbable that the albuminoids are more important as sources of the fat than the usual food-products to which it is attributed.

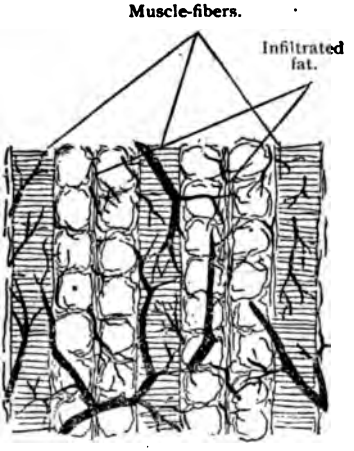

FIG. 175.— PSEUDOHYPERTROPHIC MUSCULAR PARALYSIS; FATTY INFILTRATION OF MUSCLE.—(*Flütterer.*)

Sites. — The cells normally containing fat as one of their essential constituents are first to show excessive deposit of the material when changed conditions lead to infiltration. In the liver, particularly in the peripheral zone of the liver lobule; in the general subcutaneous tissues, with the exception of the lax areolar tissues of the scrotum, eyelids, lips, alæ of the nose and ears; in the connective tissue between the muscle-fibers (pseudohypertrophic muscular paralysis); in the subserous structures; and in other connective tissues. A more or less circumscribed collection of fat constitutes a neoplasm known as a lipoma. The general infiltration of fat into an organ—such, for example, as the heart—is referred to as **lipomatosis** of the organ involved. When the infiltration of fat is extensive, constituting what might be termed a universal lipomatosis, the condition is commonly spoken of as **obesity** or **adiposity.**

Microscopically, the fat is taken up by the connective-tissue cell; the nucleus is crowded to one side, the fat existing in the cell as a single large fat-globule; in the liver tissue the fat is taken directly into the liver cell. The nuclei of the infiltrated cells are not diseased, but merely show crowding to one side. In the muscles the fat is infiltrated between, and not into, the muscle-fibers, a condition easily, differentiating fatty infiltration from fatty degeneration. It is not intended to imply that fatty infiltration is always essentially a simple process; not uncommonly it is combined with an associated fatty degeneration, the two conditions being so intermingled as to lead many observers to hold that they are essentially similar. There can be no doubt

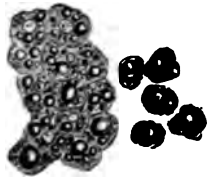

FIG. 176. — LIVER CELLS SHOWING FATTY INFILTRATION. × 250 diameters.—(*Schmaus.*)

that fatty infiltration can exist independent of fatty degeneration, and that the reverse is equally possible. As the degenerative lesion is the graver, the infiltration is less important in the mixed lesion.

2. Amyloid or **albuminoid infiltration,** also known as **albuminoid disease, lardaceous infiltration, waxy** or **bacony infiltration.** Of the many names applied to this condition, the term lardaceous offers certain advantages and has the official sanction of the Royal College of Physicians; to avoid the confusion incident to our ignorance in regard to the ultimate character of the processes it is deemed most wise to avoid calling it either an infiltration or a degeneration, and for the present to

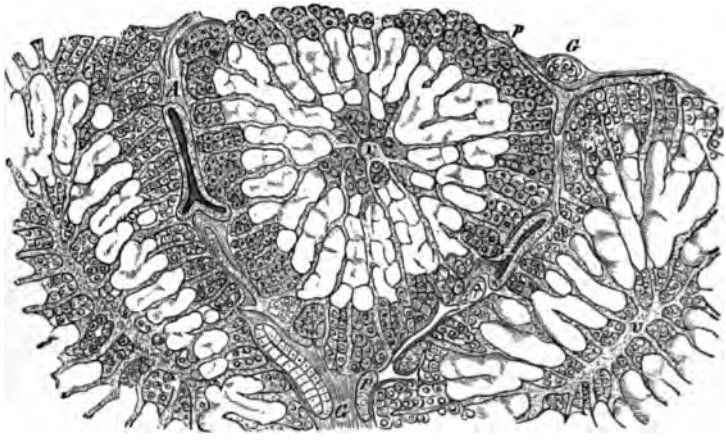

FIG. 177.—AMYLOID LIVER. (Semidiagrammatic.)

A. Branch of hepatic artery with amyloid walls. *G, G*. Bile-ducts. *p, p*. Portal veins. *v, v*. Hepatic veins. The colorless area occupying the intermediate zone of the liver lobules is, for the most part, lardacein.—(*Rindfleisch.*)

refer to it as lardaceous change or lardaceous disease. Amyloid material, or, more properly, lardacein, is found during health in the prostate gland, and has been observed in the pia mater.

Causes.—Amyloid material probably represents an altered proteid normally present in the blood—possibly fibrin, or, more correctly, the proteid body or bodies whose end is in fibrin. It can be made artificially by suspending the spinal cord in alcohol for a few months. The artificial product so made responds to the chemic tests for lardacein, and can not be differentiated from the natural material. If fresh blood be whipped, and the fibrin so obtained washed and treated with a 1 : 2000 solution of hydrochloric acid, the mass becomes gelatinous, clear, and pultaceous,

and answers all the stains for amyloid material. As amyloid infiltration commonly occurs in connection with long-standing suppuration in which the alkaline salts are drained in excess, and as the product resembles a dealkalinized fibrin, it was supposed that the morbid process naturally arose as a result of the removal of alkaline salts from the blood; this is not borne out, however, by the fact that lardaceous disease occurs in malaria and syphilis, very often unassociated with suppuration. Tuberculosis is often the cause (50 per cent. of the cases), especially bone and lung tuberculosis; anything that greatly reduces the general nutrition favors its development.

By some, lardaceous disease is regarded as a degeneration. In a sense this is true; in the blood the alteration is of the nature of a degeneration; the material itself is a degeneration product, as, probably, is melanin. As deposited in organs, it represents an additional element—an infiltration; and as the degenerative process is restricted to the origin of amyloid material, the term infiltration is applied to the deposit in organs and tissues. There is not adequate proof that, where found, it results from a degenerative change in the tissues at hand: *e. g.*, it is not probable that the amyloid liver weighing 7 kilos is the result of a degenerative change in an organ normally weighing 2.5 kilos. Wherever found, lardacein presents evidence of being an added product; but as to the method by which the addition is accomplished, we know but little. It may be that primarily there is a deposit of some body that later is converted into lardacein.

Attempts at the artificial production of amyloid infiltration by the injection of bacteria or of bacterial products into animals have not yielded uniformly successful or satisfactory results. Krawkow's experiments were unsatisfactory, in that the artificial lesions did not resemble, with any detail, the disease as seen in man. Later experiments by Davidsohn seem to have been more successful. The artificial production of amyloid disease must be considered, for the present at least, as being in the experimental stage.

Sites.—The process usually begins in the blood-vessels, deposition taking place in the intima and between the intima and adventitia, displacing, or, to a certain extent, replacing, the muscular coat. The deposit occurs almost exclusively in the arteriole, but may be seen around the capillaries, and occasionally in the larger blood-vessels. The organs most commonly involved are the liver, the spleen, the kidneys, the blood-vessels of the mucous membranes,—more particularly those of the intestines,—and the lymph-glands. Of 118 cases of lardaceous disease

observed by Dickinson, the reaction was present in the kidney in 95; in the spleen in 76; in the liver in 65; in the intestines in 35; in the stomach and suprarenals, each 9; in the lymphatic glands in 5; in the pancreas, thyroid, esophagus, testis, and endocardium, each 1.

Morbid Anatomy.—The organ is large, heavy, and pale, the paleness being due to the infiltrated material and to the anemia; the borders of the organ are rounded; it is tough in texture; decomposition takes place very slowly; the organ possesses a specific gravity very much higher than the normal. In the spleen the Malpighian bodies are largely involved, and usually show as small translucent grains, resembling boiled sago, and hence the name "sago-spleen." (For description of morbid anatomy of lardaceous disease of the liver, spleen, kidney, etc., see chapters on those organs in part III.)

Chemic Tests and Reactions of Amyloid Material.—Amyloid material is but slightly digested by pepsin, and only when presented in a finely divided state. It is soluble in ammonia and in strong hydrochloric acid, but is not dissolved by dilute mineral acids or by acetic acid, or in saline solution or in water. The iodin reaction, which is usually applied for the detection of amyloid material, is obtained as follows: A watery solution of iodin, such as Gram's solution (p. 96), is applied to the cut surface of the suspected organ, first carefully removing any blood that may be present. The amyloid material is stained a mahogany-brown, (see Plate I), while the normal tissue takes on a canary-yellow color. If a small piece of tissue be stained with iodin, as previously directed, and afterward treated with a five to ten per cent. aqueous solution of sulphuric acid, the lardaceous material will redden and eventually turn blue. Occasionally, this reaction can not be obtained, the sulphuric acid but deepening the brownish hue already given by the iodin. The fact that amyloid material does not always respond in exactly the same manner has led to the belief that we are dealing with a number of bodies so closely allied that, with the means at present at our command, differentiation is impossible.

For the histologic demonstration of lardacein the material should be fixed in absolute alcohol, the sections stained in Gram's solution, washed in water, and mounted in glycerin or glycerin jelly. Unfortunately, permanent mounts quickly lose the characteristic color. Sections may be, without previous staining, dehydrated in a mixture composed of one part of tincture of iodin and three parts of absolute alcohol, cleared, and mounted in oleum origani cretici. A number of anilin dyes

Cut surface of spleen, showing lardaceous change. The wedge-shaped area shows the iodine reaction. (*Atlas of Pathology*, Sydenham Society.)

afford reasonably characteristic stains for amyloid material. Sections are stained in a one per cent. solution of methyl-violet for five minutes, washed lightly in one per cent. aqueous solution of acetic acid, followed by water to remove the excess of the acid, and mounted in glycerin or glycerin jelly. The tissues by this method are stained blue and the amyloid material a reddish-violet. Iodin-green may be applied in the same manner, although a longer time in the stain is usually demanded; with this reagent the tissue stains green, the lardacein, reddish-violet. Birch-Hirschfeld recommends a combination of gentian-violet and Bismarck brown. Sections are first stained five minutes in a two per cent. alcoholic solution of Bismarck brown, washed in alcohol followed by water, and this in turn by a two per cent. aqueous solution of gentian-violet for ten minutes; they are differentiated in one per cent. aqueous solution of acetic acid, washed in water, and mounted in glycerin or glycerin jelly, or, best, in levulose. The tissue is stained brown by this method and the amyloid material red. Harris recommends the following method: Fix material in alcohol, stain sections three to twenty-four hours in carbol-toluidin-blue, rinse with water, and mordant for one or two seconds with a two per cent. solution of ferrocyanid of potassium, wash in water, and differentiate in acid alcohol. Dehydrate, clear in cedar oil, mount in balsam. Lardacein is stained red; other elements, varying shades of blue; the slightly reddened fibrous tissue is easily identified. In addition to the specific stains previously indicated, satisfactory exhibition of the amyloid areas is afforded by any good hematoxylin stain, followed by eosin and mounted in the usual manner. Sections so prepared keep well and exhibit both the normal and abnormal structures to advantage.

3. **Pigmentary infiltration,** also known as **pigmentation,** consists in the introduction into the tissues or cells of pigment granules. These pigment granules may arise from two sources: (*a*) They may be imported into the body, and are therefore **extraneous pigments,** or (*b*) they may arise as the result of changes in elements normally present in the body—**autochthonous pigments.** Another form of pigmentation, known as **pseudomelanosis,** has been described; it is essentially due to hydrogen sulphid coming in contact with the iron present in the tissues postmortem. It is usually seen on the under surface of the liver, and occasionally on the intestines; sometimes the spleen shows it. One knowing of its possible presence postmortem is not likely to be mistaken, or fail to recognize the condition when it is present.

(*a*) *External or Introduced Pigments.*—These are well illustrated in pneumoconiosis. (See Diseases of the Mucous Membranes in part III.) In this type are included solid pigments arising from external sources, such as hard coal in miners, iron in laborers in iron manufactories, and, in stone-cutters, particles of sand. Any of these insoluble pigments can secure access to the tissue through a wound, in which they are probably retained by the action of phagocytes. A form of this pigmentation, as it occurs in wounds, is seen in tattooing, also in the small grains of powder that may be thrust into the skin in powder explosions.

In **pneumoconiosis** the foreign material enters by way of the air-passages, and may consist of any solid body that is capable of dissemination in a sufficiently finely divided state to permit

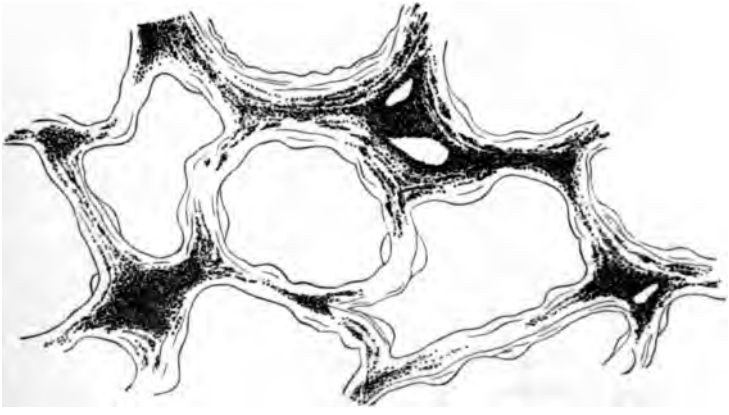

FIG. 178.—SECTION OF LUNG SHOWING INFILTRATION OF THE CONNECTIVE TISSUE OF THE ALVEOLAR WALL BY COAL-DUST (ANTHRACOSIS).—(*Rindfleisch.*)

its inhalation. When the solid material is hard coal, the condition is spoken of as **anthracosis**; when the material contains iron, the condition is known as **siderosis**; when composed of sand or of fragments of stone, as in stone-cutters, it is called **lithosis** or **chalicosis.** Once the pigment passes through the protecting membrane,—either skin or mucous membrane,—it reaches the lymphatic spaces, and may pass on to the lymph-glands, or even further, and may eventually reach the circulation. A lymph-gland may break into a blood-vessel, and the solid pigment may be carried everywhere by the circulation. Weigert asserts that this is a method by which any extraneous pigment reaches other viscera than the lung: *e. g.*, the liver and spleen.

Other extraneous pigments do not enter the body as pigments, but are converted into pigments by the action of the body-juices. Silver may be taken as a type of these pigments entering the circulation and coming to the surface of the body as an albuminate. It is deposited in the skin by the action of light as metallic silver, the resulting condition being known as **argyria.**

(*b*) *Pigments Derived from Elements Normally Present in the Body.*—Pigmentation is a normal process in the skin of the negro, and in the iris, etc. Pigments derived from the blood—so-called

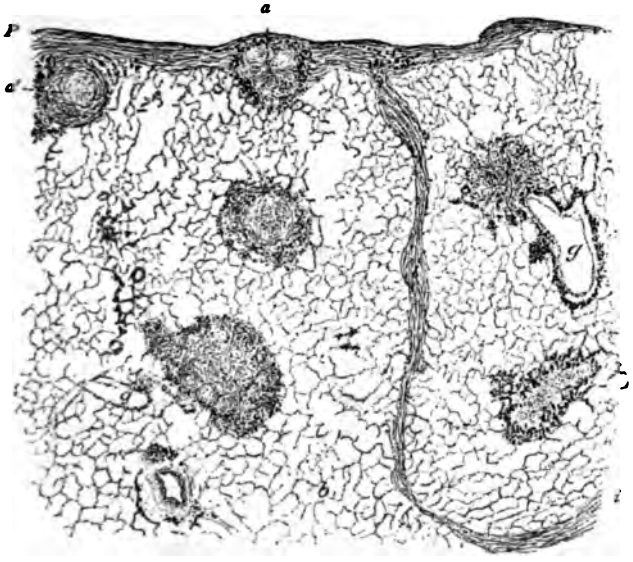

FIG. 179.—SECTION OF A LUNG SHOWING CHALICOSIS.

P. Pleura. *b.* Nearly normal air vesicles; some are slightly emphysematous. *a.* Mass of infiltrated material with dense fibrous capsule and situated in the pleura. *a'.* Similar mass in the lung tissue; other masses are shown. *g.* Blood-vessel around a branch of which is forming an area of infiltration. *i.* Thickened fibroid, interlobular septum.—(*Schmaus.*) × 30 diameters.

hematogenous pigments—are the results of changes in the normal hemoglobin during life. In health the hemoglobin is not yielded to any of the tissues with which it comes in contact; in certain conditions, however, the blood coloring-matter may be altered, as in *hemoglobinemia*, or the hemoglobin may pass off with some of the excretions, as in *hemoglobinuria*. During life the two blood pigments resulting from changes in the hemoglobin are *hematoidin* and *hemosiderin;* the latter differs in many respects from the former: the principal difference is that hemosiderin contains iron. A pigment very closely allied to the foregoing is *melanin;*

with hemosiderin, melanin forms the chief pigment of malaria. Melanin is a normal pigment in the skin of the negro and around the nipple in the white; it is also seen in tumors, where the condition is known as *melanosis;* or the tumor is said to be *melanotic;* it may be produced by the cellular activity of the part, and it may follow hemorrhage. In Addison's disease melanin is deposited in the skin of certain parts of the body; in malaria melanin may be found in the large glandular viscera, such as the liver and spleen.

When any of the hematogenous pigments are deposited in organs, the tissue affected is said to show **hemochromatosis,** a name given to the condition by von Recklinghausen. Hemochromatosis is seen in the liver, spleen, lymph-glands, bone-marrow, lungs, and kidneys, and, in very rare instances, in the mucosa of the intestine.

Jaundice.—A form of pigmentation in which the pigment is derived from blood coloring-matter, but which, at the same time, would not occur without the intervention of another process in metabolism, is jaundice. While it is true that certain blood pigments, including hematoidin, are chemically identical with bilirubin, and that the latter is abundantly formed when there is rapid hemolysis, still, there is not sufficient reason for believing that this production is ever sufficient to give rise to jaundice. Bile pigment is produced in the liver, and by reabsorption enters the circulating blood, and is the agent that produces the discoloration of the various tissues so markedly influenced in jaundice. The pearly white of the conjunctiva is usually first to manifest the discoloration; afterward we see all of the tissues more or less discolored.

Commonly, the brain and spinal cord escape pigmentation. It is said that the gastric and pancreatic secretions do not show the yellowish tinge. With regard to the sources of the pigment circulating in the blood two views have long been in force, these leading to the recognition of two forms of jaundice, one hepatogenous and the other hematogenous.

Hepatogenous jaundice is presumed to depend upon the production of bile pigment in the usual way, and its absorption by the blood as a result of retention within the biliary channels. This retention may depend upon swelling of the mucous membrane of the duct, biliary calculi, tumors within or without the duct and pressing upon it, inflammatory adhesions, kinks, pressure by a misplaced viscus, such as the right kidney, parasites in the bile-duct, etc. The resorption of bile as a result of such obvious obstructions as those just considered deserves no special comment. There are forms of jaundice, however, that are not obstructive in

the sense previously indicated. It is alleged that jaundice may depend upon the overproduction of bile (polycholia); the abnormal bile may be viscid, slow-flowing, and hence offer opportunities for resorption, or, entering the intestine in large quantities, it may be taken up by the portal circulation and returned to the liver, which may not be equal to the continued removal of the pigment from the blood, which, escaping the hepatic cells, passes onward into the general circulation.

Hematogenous jaundice is seen in connection with various morbid processes in which blood destruction constitutes an important element. It is the erythrocytolysis of yellow fever, pyemia, pernicious malarial fever, and allied diseases that causes the form of jaundice in question. The jaundice associated with venom-poisoning, phosphorus-poisoning, etc., belongs with this group. The fortunate possession of an agent (toluylenediamin) destroying the blood and bringing about this form of jaundice has enabled investigators to study the changes that accompany the condition. It has been shown that destruction of the blood-cells leads to the production of a bile whose viscosity prevents rapid flow through the biliary capillaries, and hence permits regurgitation, or at least increases biliary pressure to an extent compatible with resorption. At the same time there is more or less catarrhal swelling of the mucosa of the biliary passages, which further impedes the flow. The jaundice is then truly obstructive, and not actually of hematogenous origin, although the initial step in the process was probably the erythrocytolysis. Experimental studies of the jaundice produced by phosphorus and arseniureted hydrogen offer conclusive evidence that the production is due to the same conditions as toluylenediamin jaundice. Further, it has been shown that if the liver is removed and poisoning by some of the before-mentioned agents brought about, blood pigments appear in the urine, though bile pigments are not found.

Jaundice is not properly considered with the infiltrations of pigment: it is more truly the diffusion of a soluble pigment. Its action, however, on many cells closely resembles that of insoluble pigments.

There is a form of pigment known as *hemofuchsin*, seen in the heart muscle, and occasionally in unstriped muscle, having been noted mostly in the muscular layer of the jejunum. The chemic characteristic of hemofuchsin is that it does not contain iron, and, therefore, resembles hematoidin; its color is of the brightest red, and the granules are finer than hematoidin. Its source has not been definitely determined.

A pigment closely allied to hematoidin is *lutein*, which is the

coloring-matter of the yolk of the egg, and is found in the corpus luteum.

There are a few pigments that do not enter the body as such, but are developed in the body from elements not normally present; as an example of these we have the pigmentation following the administration of silver, *argyria*, to which reference has already been made.

Bacterial Pigmentation.—Certain pigments produced by bacterial growth occur in suppuration. The bacillus pyocyaneus is the organism most commonly producing pigment in pus, or even catarrhal discharges from such mucous surfaces as the nose, uterus, and, rarely, the bowels.

Occasionally, the cells whose particular function it may be to elaborate given pigment fail to do so. Such failures often become as conspicuous and as easily recognizable as the overproduction of pigment under other circumstances. The **albino** is an example of congenital absence of pigment production, particularly in the skin, the hair, the irides, and the choroid coats of the eyes. A minor degree of failure in pigment formation is seen in the condition spoken of as **leukoderma**, in which whitish areas appear upon a skin otherwise normal. Occasional instances of this peculiar disorder have been observed in the colored race, the skin at times showing areas of snowy whiteness, which strongly contrast with the surrounding normal areas. No satisfactory explanation of this condition is at present forthcoming. The failure in the production of blood pigment seen in certain blood diseases, probably deserves a separate classification.

Demonstration of Pigment in Tissues.—With the usual processes of fixation most pigments can be readily recognized within and between the cellular elements of the areas involved, but their identification is a more difficult task. The chemic and microchemic reactions of the various pigments are but poorly understood. In addition to the differentiating points previously indicated, the most important demonstration is that of iron. As before stated, hemosiderin contains iron; there are probably a number of pigments included under the name of hemosiderin merely from the fact that iron is present. The demonstration of the iron is usually accomplished as follows: Tissues that have been fixed in absolute alcohol are sectioned in the usual manner. Sections are treated for from one to two hours in a one per cent. aqueous solution of the ferrocyanid of potassium, and mounted in glycerin containing 0.5 per cent. hydrochloric acid. The pigment containing iron, not in the so-called concealed or masked form, will show the bright blue reaction. In order to secure the reac-

tion with both ferric and ferrous salts it may be necessary to use a mixture of ferrocyanid and ferricyanid of potassium, each 0.5 to 1 gm. to 100 c.c. of water.

4. Calcareous infiltration or **calcification** consists in the deposition in the tissues of salts of lime and magnesium; the lime salts are the phosphate, carbonate, chlorid, and fluorid; the magnesium salt is a phosphate.

The term **petrification** or **petrifaction** has been applied to deposits composed purely of magnesium and other than lime salts, while the term **calcification** has been restricted to lime salts. That so sharp a differentiation is advisable or even possible is, in the opinion of the writer, doubtful.

Causes.—Calcification is practically never a primary process; most frequently it is secondary to some destructive change in the cellular elements of the area involved: *e. g.*, local changes in nutrition, coagulation of albumin, slowing of the circulation, inflammation, and chronic infections. It may be said, in a general way, that calcification is an evidence of age, and that the more marked the calcification, the older the particular tissue involved must be. Calcification is one of nature's methods of limiting infection, as is shown by the calcareous masses that collect around tubercular areas and in actinomycotic masses and in the fungus itself. The ultimate cause of the deposit of lime salts may be said to be unknown. The fact that it is more or less constantly associated with tissue death, or senescence, would indicate that disorganization or dissolution of proteid bodies favors the deposit; for this reason it has been held that the tissue elements in process of disorganization enter into chemic combination and retain within them the earthy salts, which, under normal conditions, escape or remain in solution.

Morbid Anatomy.—The lime salts may form distinct concretions, as in tubercular abscesses and tubercular glands, or they may be diffused between or into the cellular elements of a tissue: *e. g.*, the cartilages of the ribs. This latter process is analogous to ossification observed in bone; calcification differs from ossification in that the former does not have any distinct histologic structure.

Seats.—"Healed-in" infectious processes, or where attempts at "healing in" have been made; it also occurs in the cartilages: *e. g.*, those of the ribs; it is frequently present in cicatricial tissues, particularly in those connected with the periosteum; it is seen in certain tumors,—*e. g.*, psammoma of the brain,—in thrombi, and in areas that have undergone hyaline, fatty, and possibly other degenerative and necrotic processes. The salts may be deposited

both within and between the cells. Deposit within the cells is met with in the ganglion cells of senescence, but elsewhere the process is most commonly between the cells: that is, in the intercellular substance. Calcification following attempts at repair is seen secondary to inflammation of serous membranes, notably of the pleura and pericardium. It occurs as a sequence of inflammatory and degenerative processes in the blood-vessels, particularly the arteries, and is also seen around the cardiac orifices and in the older sclerotic areas in valve leaflets. One of the remarkable instances of calcific deposit is that occasionally seen in the dead fetus of a ruptured ectopic gestation. In the course of years a fetus remaining in the abdominal cavity may be extensively infiltrated with lime salts, thereby producing a body spoken of as a **lithopedion**. Calcification of the placenta is occasionally observed.

The *demonstration* of calcific deposits does not commonly require any other aid than the gross examination. The deposits are usually sufficiently well marked to be readily recognized by palpation, and may be further shown by the occurrence of fracture on bending—a test particularly applicable to blood-vessels and valve leaflets. In sections the calcific deposit is not uncommonly first discovered by the nicking of the microtome knife. When the deposit is scanty, the fine granules or grosser collections may be readily recognized under the microscope. The strong affinity of the salts for hematoxylin also constitutes an important test. The application of a five per cent. aqueous solution of hydrochloric or nitric acid leads to their disappearance, the carbonates effervescing as a result of the liberation of the carbon dioxid. The demonstration of lime salts may be further made by the addition of sulphuric acid, which leads to the formation of gypsum (sulphate of lime), which may be recognized as needle-like crystals. (See Fig. 110, p. 129.)

Uric Acid Deposits.—With gout is associated the abundant deposit of uric acid and its salts, particularly in connection with the joints, although the kidneys, skin, and fibrous tissues of the body are also likely to be involved. Wherever the deposit takes place there is usually a surrounding area of local necrosis, or at least marked degenerative changes. The cause of the deposits has not been definitely determined. We do not even know whether it is defective excretion, overproduction, or faulty oxidation. The deposition is frequently associated with local pain and inflammation. The statement commonly made that the deposits consist of sodium urate is not strictly true, as Roberts has satisfactorily demonstrated that they are composed of sodium biurate,

probably precipitated in the tissues involved from the quadriurate circulating in the blood. The uratic deposit in the cortex of the kidney is irregularly distributed, while in the medullary portion it follows the course of the straight vessels. The **tophi** in the cartilaginous external ear (the helix), the deposits in the eyelids, around the tendons, in the fibrous textures of the palms of the hands and plantar tissues are composed of inflammatory, necrotic, and hyaline elements containing a varying amount of sodium biurate.

5. Glycogen Infiltration.—Glycogen, like fat, is a normal constituent of liver tissue, arising from the metabolism of grape-sugar by the extraction of a molecule of water:

GRAPE-SUGAR.		WATER.		GLYCOGEN.
$C_6H_{12}O_6$	—	H_2O	=	$C_6H_{10}O_5$

That it can also be produced from albumins there seems no reasonable doubt; but the uncertain composition of the proteid bodies makes the chemic change of albumin into glycogen an unsolved problem in physiologic chemistry. While produced normally in the organism, it is in diabetes that we see its most remarkable generation. When we have solved the pathology of diabetes, the production of glycogen, and particularly its tissue infiltrations, may become apparent. It has a rather remarkable resemblance to amyloid material, and still, that it is not the same, can be easily established. It reacts with an aqueous solution of iodin very much as amyloid material, but does not give the blue with iodin and sulphuric acid; if treated with ptyalin or amylopsin, it quickly loses its iodin reaction; while amyloid is insoluble in water, glycogen is freely soluble. Glycogen is converted postmortem into grape-sugar. The extraction of glycogen from the liver is accomplished by dissolving it in an alkali and precipitating by alcohol. It is a white powder, freely soluble in water, giving the solution an opalescent tint.

Demonstration.—To demonstrate glycogen in the tissues, use anhydrous alcohol for fixation, infiltrate with celloidin, and harden in cedar oil and chloroform. (P. 61.) For staining, Barfurth advises a glycerin solution of iodin, and Ehrlich a syrupy solution of iodin in gum acacia. By either of these solutions it stains brown, like amyloid, but is differentiated by the insolubility of the last-named body. Fixation in absolute alcohol lessens its solubility but does not render it insoluble. It does not give the blue reaction with iodin and sulphuric acid, as lardacein may do.

As an infiltration, glycogen is found in the liver, epithelial cells of Henle's loops, in leukocytes and pus-cells, in tumors (particu-

larly carcinoma and adenoma of the testicle), in sarcoma of bone, and, rarely, in similar tumors in other situations. It is present in the leukocytes in diabetes, and it is claimed that the diagnosis of diabetes can be made, before sugar appears in the urine, by the glycogen reaction of the white cells.

Morbid Anatomy.—Organs showing glycogenic infiltration resemble amyloid organs with the following exceptions: The specific gravity is low; there is not the bacony density; anemia and brittleness are less marked; the organs never attain the size sometimes seen in amyloid disease; and the difference given above in the chemic stain reaction.

Cholesterin Infiltration.—There is much doubt as to this being an infiltration; in degenerative processes cholesterin is likely to be found, but gives no macroscopic evidence of its presence. Under the microscope it may be recognized as thin, rhombic plates with not very regular edges, and quite commonly a small square out of one corner, appearing as though it had been cleanly cut out. (See Fig. 115, p. 130.) In addition to the degenerative processes already mentioned, cholesterin is found in the contents of cysts, and sometimes in inflammatory exudates and in atheromatous areas.

Hydropic Infiltration.—In edema the tissues involved are bathed in the fluid that distends the lymph-spaces, and the cells of the area may take up a varying amount of this fluid. By some this is considered an infiltration, and is spoken of as dropsical or hydropic infiltration. It is practically always associated with more or less degenerative change in the cells, and it has, therefore, seemed to the writer best to consider it with the degenerations. (See Edema.)

(B) DEGENERATION.

Degeneration implies that the cellular elements of an organ are undergoing or have undergone such changes, both chemic and structural, as to preclude their proper maintenance of function; degeneration differs from infiltration in that infiltration is something carried to the organ or cell and deposited, or something manufactured by the cell and retained, while degeneration implies that the cell, including its chemic and physical elements, has undergone important nutritive changes, which may be entirely independent of any extraneous material brought to the organ involved. Infiltration may lead to degeneration, and degenerations may be accompanied by infiltrations; the processes are, however, distinct. Notwithstanding the entity of each, an infil-

tration may be associated with a degeneration, the two processes apparently going on side by side, thus affording an obscure picture of both. In such complex processes, however, the degeneration is likely to be the lesion that is most detrimental, and while it may have been preceded by the infiltration, or the infiltration may have arisen after the inception of the degeneration, still, the degenerative lesion will constitute the important pathologic phenomenon. Degenerations are also known as **metamorphoses**; occasionally a degeneration is spoken of as a **necrobiosis**; this term is not, however, correct, as the latter condition implies molecular death, and an organ may be degenerated or a cell may be degenerated and may not as yet be dead, although ultimately the cell may perish. The degenerations are parenchymatous, fatty, hydropic, colloid, mucoid, and hyaline.

1. **Parenchymatous degeneration,** also known as **cloudy swelling, granular degeneration,** and **parenchymatous metamorphosis,** consists of a precipitate, within the cell protoplasm, of what seems to be albumin, or other cell proteid, in a finely granular form. The nucleus of the cell is obscured, or even hidden, by minute granules, and, late in the process, may be destroyed; the perinuclear protoplasm contains an abundant granular precipitate; the cell outlines are indistinct, and the entire body may be disintegrated. It is probable that the process, if continued, terminates in a fatty degeneration, and that the granular bodies seen are eventually converted into oil. The cell may again be cleared up by the use of dilute acetic acid or a strong alkali. The nucleus will again become visible, although the granular bodies may merely agminate and not disappear.

Causes.—High temperature; poisoning by carbonic, phosphoric, and arsenious acids, and by the salts of mercury, copper, antimony, etc.; intense or long-continued hyperemia, vascular stasis, and edema; inflamed mucous membranes usually show it to a high degree; a similar process is seen in inflammation of muscle: *e.g.*, acute myocarditis; in acute yellow atrophy of the liver many of the cells will be found granular and many of them fatty to a high degree; any malnutrition may simulate the condition, and many poorly nourished gland-cells, particularly in atrophic processes, show the change. Bacteria and their products, as well as other organic poisons,—the latter due to faulty metabolism or deficient excretion, or to combinations of both processes,—venoms, etc., are also causes.

Morbid Anatomy.—The organ is swollen, increased in size, cloudy or opaque on its surface, appearing cooked, softer than normal, and, when the process is simple, there is evidence of

anemia, but, as commonly seen, there is an increased amount of blood in the part: *e. g.*, the cloudy swelling seen in the kidney may be the initial stage of inflammation, and the organ, under such circumstances, will be distinctly hyperemic.

Termination.—If the cause be early withdrawn, it is probable that recovery of the cell may occur; if the cause continue to act, fatty degeneration ensues, the cells are destroyed, and new cellular elements must be produced by the undestroyed tissue elements or the connective tissues.

Demonstration.—The alterations previously described in the gross organ usually enable one readily to recognize the condition. The examination of fresh cells obtained by scraping the surface of the tissue involved may offer confirmatory evidence, to be considered with the gross appearance. Too much confidence, however,

FIG. 180.—CLOUDY SWELLING OF THE EPITHELIAL LINING OF THE KIDNEY TUBULE.—(*Flüttlerer.*)

FIG. 181.—GRANULAR DEGENERATION OF A MUSCLE-FIBER, LAST STAGE, NEARLY FATTY.—(*Schmaus.*)

FIG. 182.—CLOUDY SWELLING OF THE LIVER CELLS. × 250 diameters.—(*Schmaus.*)

can not be placed in the examination of detached cells. In such cells the granules clear up or agminate when treated with a one per cent. aqueous solution of acetic acid. They are not soluble in alcohol, ether, chloroform, or other agents that dissolve fat, nor are they blackened by osmic acid. Pieces of the organ under observation should be fixed in an osmic acid solution (see pp. 48 and 49), infiltrated with celloidin (paraffin is not applicable), and sectioned in the usual manner. The granules are not blackened by this process. Tissue fixed in corrosive sublimate or in Zenker's fluid (see pp. 49 and 50), sectioned, and stained with hematoxylin and eosin will commonly show the alterations to advantage. The intensity with which the granules take the acid anilin dyes is always to be remarked.

2. Fatty Degeneration.—This probably represents but a later stage of the preceding. In the cells, at this stage of the process,

the granular bodies, before noted, are converted into minute oil drops; the nucleus is destroyed and can not be made to reappear; the cell is shrunken and not swollen; its outlines are apt to appear irregular, or evident cell dissolution may be manifest. The oil drops usually do not run together as in fatty infiltration. The compound granule cells in brain softening represent a type of fatty degenerated cells. The cellular debris is usually manifest.

Causes.—(1) The causes already given for cloudy swelling; (2) anemia; (3) some of the forms of necrosis are accompanied by fatty degeneration: *e. g.*, caseation. Total or circumscribed fatty degeneration usually results from embolism, infection, or the noxious influence of bacterial toxins and allied agents.

Morbid Anatomy.—As soon as the removal of fat by absorption begins, the organ diminishes in size, becomes soft, almost pultaceous, feels oily, and greases the knife with which it is cut. The organ is paler than normal, yellow in color, markedly anemic, and may show interstitial or parenchymatous hemorrhage due to the degenerative processes involving the capillaries. The color of the organ may not be uniform, but mottled, as a result of the process being more active or more marked or at a later stage at some points. The color is also influenced by the amount of blood in the organ and by the presence or absence of hemorrhage or of associated pigment. The conversion of the proteid matter into fat leads to a reduction in the specific gravity. The parenchymatous cells show the alteration earlier and in a more characteristic manner than the connective-tissue elements, which may escape. When the process is focal and marked, and in certain tissues,—as, for example, the central nervous system,—the softening may go on to complete liquefaction. (See Softening of the Brain.)

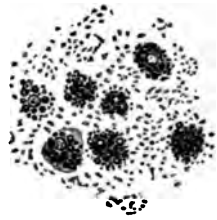

FIG. 183.—FATTY DEGENERATION OF THE LIVER CELLS. × 250 diameters.—(*Schmaus.*)

Sites.—Epithelial surfaces and glandular viscera, muscles, nerves, and blood-vessels; occasionally observed in the brain, and there constitutes a variety of softening. In certain localities the process is apparently physiologic: for example, the production of fat by the breaking down of the central cells of the acini in the mammary gland leading to the formation of milk, and the fatty change seen in the uterus after labor. (See Fatty Degeneration of the Heart, Blood-vessels, Liver, etc., part III.)

Demonstration.—The highly refractive oil globules can usually be recognized under the microscope. In fresh tissues they are

not cleared up by acetic acid; they are blackened by osmic acid; the black or brownish-black granules produced by treating fat with osmic acid are not soluble in alcohol during the subsequent dehydration, but may undergo solution during the process of clearing for paraffin infiltration, and particularly during the treatment by fat solvents, such as chloroform, turpentine, xylol, etc. For the demonstration in sections fixation in alcohol is not applicable. Tissues should be fixed in one of the osmic acid solutions (see pp. 48 and 49), dehydrated, infiltrated with celloidin, and sectioned. The fat globules will be blackened by this method. Blocks of tissue may be fixed in Müller's fluid (see p. 49) or in Orth's fluid (see p. 50) or in a ten per cent. solution of formaldehyd for a week or ten days. The tissue is then transferred to Marchi's fluid, which consists of:

Müller's fluid, ... 2 parts.
One per cent. aqueous solution of osmic acid, 1 part.

The tissue is permitted to remain in this solution for a week or ten days. For successful treatment the blocks of tissue should be very small—not over two to five millimeters in thickness. Embedding in celloidin is permissible. After cutting, the sections are cleared in cedar oil and mounted in balsam without staining. The fat globules will be black or brownish-black. When desired, sections may be stained in the usual manner, which will permit an examination of the nuclei and of the associated structures to advantage. Paraffin infiltration does not yield so satisfactory or trustworthy results as celloidin, as the preliminary clearing agents are liable to extract a part of the fat.

3. Hydropic degeneration (cellular dropsy, cellular vacuolization) is practically an intracellular edema. The affected cells are very much larger than normal, and contain many so-called vacuoles, usually in the perinuclear protoplasm, although the nucleus may be involved. The evident cell damage is less than in parenchymatous degeneration, but may be most marked when the two processes are associated, as is not uncommonly the case.

Causes.—Edema, inflammation, infectious processes, and degenerative lesions in general when affecting the large ganglion cells of the central nervous system.

Sites.—Epithelial surfaces, particularly the mucous membranes, glandular viscera in inflammation and edema, edema of the muscular tissues in which many fibers are swollen and, on transverse section, show extensive central vacuolation. The morbid anatomy is practically that of edema, but hydropic degeneration is often present when no gross lesion is manifest.

Demonstration.—No specific method has as yet been devised for the demonstration of this process. Rapid and powerful fixatives are demanded in order to prevent the cell from emptying itself of the fluids, before fixation is completed. Probably the best results are obtained by fixing small pieces of the tissue in corrosive sublimate (see p. 49), followed by hematoxylin and eosin staining.

4. Colloid degeneration is a process by which cellular protoplasm is converted into a homogeneous, gelatinous, structureless mass. The exact cause of this change is not known; it occurs in connection with epithelial cells, to which it is practically restricted. It is, therefore, a common phenomenon in glandular structures where exit is prevented by occlusion of the duct; it is seen in the kidney and in ovarian cysts; it occurs in goiter and in cancerous masses. The constancy with which it is found in the thyroid gland has led many observers to believe that it is a normal constituent of that organ, and, when greatly increased in amount, the condition is spoken of as colloid goiter. The exact chemic nature of the material has not been definitely settled; it is not precipitated by alcohol or acetic acid, it is insoluble in water, and is not rendered opaque by chromic acid.

Macroscopically, the material is gelatinous, stringy or ropy, and is usually colorless, but may be slightly bluish or yellow.

Microscopically, it will occasionally be observed to be arranged in concentric masses. It does not stain well with the anilin dyes, but stains with carmin.

Colloid degeneration of muscle has been described by Zenker, and is closely allied to the hyaline degeneration, which he also describes. Colloid material is found in some cancers, particularly in those of the alimentary canal; it is also found in cysts possessing an epithelial wall. Colloid transformation occurs in the cerebral vessels, where, according to Mallory, it is particularly subject to subsequent calcareous change. (For demonstration and differentiation from amyloid, mucoid, and hyaline material see paragraph following Hyaline Degeneration.)

5. Myxomatous degeneration, also known as **mucoid degeneration** or **myxomatous metamorphosis:** Myxomatous material is normally found in Wharton's jelly and in the vitreous humor. The process terminates in the formation of a semifluid, hyaline body containing a varying quantity of mucin. A further study of mucin has led to the recognition of the fact that what was originally considered to be a chemic entity is now found to occur under a number of conditions and in more than one form. In epithelial structures the mucin exists in the mucus elaborated

within certain of the cells, which assume, as a result of the accumulation in their interior, a goblet form, and hence are called *goblet cells*. The free end of the cell opens and the accumulated contents flow out, the cell returns to its normal shape and resumes the manufacture of mucus. In other instances the cell is actually shed, undergoes dissolution, and liberates the elaborated product. During inflammatory processes in epithelial surfaces the quantity of mucus thrown off is increased. The production of mucoid material is not, however, restricted to the epithelial tissue, but is intimately associated with the connective tissues, and arises from the transformation of the cell, or, more frequently, and probably more truly, of the intercellular substance into a jelly-like material containing mucin. Chemically, the material seems to be made up of complex albuminous compounds in which mucin is abundantly present. The affected area is gelatinous and trembling, almost perfectly clear, and colorless.

Microscopically, mucoid material is quite homogeneous, and not uncommonly contains large multipolar cells with long, branching filaments. These form a reticulum, which supports the gelatinous material and maintains its conformation; it is not arranged in concentric masses, like colloid material. Mucoid material is precipitated by alcohol and acetic acid, and is best fixed by corrosive sublimate. It will absorb considerable water, which causes it to swell; it does not, however, undergo solution. It is dissolved by neutral salt solutions and by alkalies, even in comparatively weak solutions. (For further remarks on demonstration see paragraph following Hyaline Degeneration.)

Sites.—As before indicated, *mucoid degeneration* occurs in both connective and epithelial tissues; it is present in certain connective-tissue tumors, most commonly in myxoma and lipoma, occasionally in sarcoma or chondroma, and rarely in carcinoma.

6. Hyaline degeneration, also known as **vitreous** or **glassy degeneration** or **hyaline metamorphosis.** The exact nature of the material produced, and the method by which it is elaborated, have not been worked out; the body seems closely related to colloid material, but is firmer, more fragile, and arises in a different class of tissues; it is most commonly found in the lymphatic glands and blood-vessels and capillaries, around which it may form a distinct mantle; it is occasionally observed just outside the intima of the blood-vessels and around the capillaries, thus closely resembling amyloid material. It does not, however, give the amyloid reaction. Hyaline material is occasionally observed in the brain, in the stroma of epithelial tumors, and in the

dendritic filaments of papilloma of the bladder and other mucous surfaces. The degenerative change observed in the muscles in typhoid fever, particularly in the abdominal recti and the muscles of the upper portion of the thigh, has been variously placed. By some it is regarded as a special degenerative change restricted to muscle; by others it is grouped with the hyaline degenerations; while still others regard the change as a form of coagulation necrosis.

Amyloid, colloid, mucoid, and hyaline materials are closely allied bodies. Thoma, von Recklinghausen, and Graham regard each as representing but different stages in the evolution of the same body. Lardacein apparently presents sufficiently distinct reactions to entitle it to be considered alone. That the remaining conditions are separable by methods at present at our disposal seems doubtful. Differentiation by stain reaction—the only method at present available—is not fully characteristic or always satisfactory. Hyaline and colloid materials seem to select acid stains, while mucoid is commonly best stained by basic dyes. Pianese differentiates these materials by fixing small pieces of tissue (2 mm. thick) in a mixture composed of 15 c.c. of a 1 per cent. aqueous solution of chlorid of platinum and sodium; 5 c.c. of a 0.25 per cent. aqueous solution of chromic acid; 5 c.c. of a 2 per cent. aqueous solution of osmic acid; and one drop of chemically pure formic acid. After thirty-six hours' fixation the tissues are washed in flowing water and transferred to eighty per cent. alcohol. Sections are stained for half an hour in the following solution:

Martius yellow,	0.01	gm.
Acid fuchsin,	0.1	gm.
Malachite green,	0.5	gm.
Distilled water,	150	c.c.
Alcohol (96 per cent.),	50	c.c.

After staining, wash in absolute alcohol, treat with xylol, and mount in xylol balsam. By this method mucin is stained sky-blue; hyaline, brick-red; colloid, bright green.

CHAPTER IV.

NECROSIS.

Necrosis is the local death of a part, as distinguished from somatic death. When necrosis of tissue results from trauma applied directly to the tissue, it is known as **direct necrosis**; when the change is dependent upon causes applied through the circulation, innervation, or degenerative processes, it is called **indirect necrosis.**

Causes.—Anything that destroys the vitality: *e. g.*, burns, scalds, and chemic destruction or injury sufficient to interfere with nutrition. The influence of trauma need but be mentioned, as the extensive laceration of the cells, with the associated disturbances of circulation, both hemic and lymphatic, makes cellular death inevitable. The action of poisons in the production of necroses is not always so apparent. There can be no doubt that of the many poisonous agents possessing the power of producing necrosis their activity is, to a certain extent, selective, some acting upon one kind of tissue and others upon dissimilar structures. Of the many poisons endowed with the property now under consideration, certain of them are inorganic, such as mercury, phosphorus, copper, arsenic, etc.; others are organized poisons, which may be again subdivided into at least three groups: (1) Vegetable poisons (from the higher forms of vegetable life many bodies might be mentioned: *e. g.*, oil of mustard, abrin, ricin, etc.), bacteria, and bacterial poisons, such as the toxin of the bacillus diphtheriæ; (2) poisons belonging to the animal kingdom, such as those elaborated by poisonous reptiles; (3) certain poisons produced by the tissues themselves. As an example of the noxious influence of the last group, it is but necessary to refer to the extensive hepatic necroses that occur in uremia, and in that particular form of intoxication known as eclampsia. The association of inflammation with necrosis may be either primary or secondary: that is to say, necrotic processes may give rise to or may be followed by inflammation; on the other hand, inflammation is always associated with a varying degree of necrosis. Obstruction to the circulation—arrest of the arterial influx, capillary flow, or of the venous exit—may cause necrosis; lymphatic obstruction may have practically the same effect; capillary **stasis,**

thrombosis, or rhexis is usually followed by necrosis of the tissues involved.

As nutrition is, in part, governed by the trophic nerves, it is held that certain necrotic changes result from lesions of these nerves or the central nervous system acting through them. Such necrotic processes are known as **neuropathic necroses.**

The cause of any given necrotic process may have been complex, more than one element, and in some instances many elements, entering into its formation. In the weak and debilitated, after fevers, in malignant diseases, and, in certain instances, following profound shock, necrotic changes are induced by injuries and other causes that, in the physically strong, would give rise to but little or even no alteration in tissue. As examples of necrosis arising in part through such influences, **marasmic** and **senile necroses** may be mentioned.

Results.—The tissue involved may undergo (1) regeneration or the nearest approach thereto, repair; (2) absorption, more or less complete; (3) retention in some form or another; or (4) it may be discharged. The possibility of associated or subsequent inflammation is not to be forgotten.

1. Regeneration and Repair.—In some instances the necrosed elements are thrown off or absorbed, and adjacent cells or embryonic constituents of the tissues involved may produce new tissue structurally and physiologically identical with that lost, in which case the lost structures are said to be regenerated. More frequently, absorption of the liquefied elements occurs, and repair proceeds to the formation of cicatricial tissue, which remains as a scar marking the point of the original lesion.

2. Absorption is only possible when the liquefaction can be complete and when bacteria do not gain access; such absorption is typified in bruises in which the extruded blood-cells are, in time, completely removed.

3. Retention.—The entire mass may be retained, or partial absorption and reparative changes may leave but a part; thus, if an infarct cut off the blood supply in a branch of the renal artery, the area involved—say, a part of a pyramid—dies; after certain degenerative processes, leukocytes and fixed connective-tissue cells wander in and convert the mass into embryonic tissue, from which granulation tissue is evolved and eventually cicatricial tissue (organization). Only a part of the involved tissue may be retained, and this may be much altered: *e. g.*, in the blood cyst, or hematoma, a fibrous capsule may be formed surrounding the escaped blood. Some of the fluid contents may be removed by the absorbents, and the remaining solid material, consisting of the clot

and cellular elements, becomes permanent, or degenerative changes may convert the mass into a cyst.

4. Discharge.—The necrotic mass may be thrown off, as in gangrene, or it may be slowly disintegrated, as in suppuration, ulceration, and caries.

Forms of Necrosis.—Liquefaction necrosis, coagulation necrosis, fat necrosis, cheesy necrosis, sphacelation *en masse*, or gangrene.

1. **Liquefaction** or **colliquative necrosis** arises as the result of infection, particularly by pyogenic organisms and irritants that are not sufficiently active to produce coagulation necrosis. It differs from coagulation necrosis in the absence of coagulation; there is the same infiltration of the tissues with fluid, but coagulation does not occur. Pus production resulting from infection represents a type of liquefaction necrosis, in that bacterial products liquefy the intercellular substance that holds the embryonic cells, and thus convert the area involved into a liquid. Liquefaction necrosis is sometimes seen to follow coagulation necrosis, and coagulation of previously liquefied areas is occasionally observed.

Morbid Anatomy.—The gross appearance depends largely upon the tissue involved, and, to a certain extent, upon the cause. The increased amount of fluid in the part may make it softer than normal—indeed, it may fluctuate; in other situations the associated increased tension gives rise to apparent induration, which disappears on incision or puncture permitting the escape of some of the fluid. In the absence of coloring-matter and blood pigment or its derivatives, the color is lighter than the normal. Concurrent fatty degeneration leads to the presence of minute oil drops,—an emulsion,—which may give the softened area a greasy appearance. Histologically, the structural elements pass through hydropic, fatty, and other degenerative processes, and, finally, may no longer contain a single normal constituent. Absorption, retention in part or as a whole, and discharge are possible terminations; repair, more or less complete, occasionally occurs, but regeneration is extremely rare, if even possible.

Site.—Fluid exudate in burns, vesicles, etc.; softening in central nervous system; secondary liquefaction of coagulated exudates, as in croupous pneumonia, and of blood-clots and thrombi.

2. **Coagulation necrosis** occurs as the result of infection; as a result of embolism or capillary plugging; in areas of interstitial hemorrhage and in blood-clots, the mass undergoes coagulation necrosis. The tissues are matted together with fibrin, which entangles whatever cellular elements may be present. When occurring in superficial structures, as on or in the mucosa in diphtheria, the fibrin found may be hyaline or homogeneous, fib-

rillar, and in some instances granular. The view at one time held that fibrin of the blood was essential to the process, is now admitted to be incorrect, as lymph containing fibrinogen may induce the change. Zenker's degeneration of muscle is, by some, held to be a form of coagulation necrosis. As an example of coagulation necrosis following infection may be mentioned its occurrence in diphtheria, tuberculosis, typhoid fever, and allied conditions. It does not seem that bacteria at the point of necrosis are necessary, but that the process may be engendered by the activity of bacterial products; that it is due to the chemic agents is shown by the intravascular injection of *abrin* or *ricin*, which is followed by coagulation necrosis in various organs. After the tissues are matted together by fibrin, fragmentation of the nuclei and more or less complete dissolution of the cells occur. In active inflammatory processes, or in the tissues immediately adjacent, coagulation necrosis is nearly always present. It not uncommonly precedes caseation, and may be present in the neighborhood of caseous areas.

Morbid Anatomy.—Early in the process the tissues become very much firmer than normal; not uncommonly the area can be recognized by palpation, even when situated some distance beneath the surface. Upon incision the freshly cut surface may resemble the opaque, glassy appearance of cloudy swelling. Later, softening not uncommonly occurs, which may progress to liquefaction. In the absence of blood or of blood coloring-matter or its derivatives, the area is lighter than normal. Histologically, the cell outlines soon disappear and the normal microchemic reactions are altered. The nuclei at first stain very faintly with the basic dyes, but later not at all, and just before complete dissolution of the cell its entire structure may take only the acid dye. Occasionally, however, even late in the process, fragments of nuclear chromatin may be irregularly disseminated through the area, and may show as irregular granules taking the basic dye in the midst of a fine granular mass that selects the acid stain. By suitable methods the presence of fibrin can be shown at some stage in the development of the process.

For the purpose of demonstrating the presence of this body Weigert's fibrin stain is recommended. Sections of alcohol-hardened tissue are fastened to the slide by an approved method. The subsequent staining is conducted as follows:

Anilin gentian-violet solution (see p. 94), two to ten minutes; rinse in normal salt solution; * apply solution of lugol (iodin, 4

* Sodium chlorid, 0.75 per cent. in water.

parts; iodid of potassium, 6 parts; water, 100 parts); rinse in water; blot with filter-paper; differentiate in a mixture composed of anilin 2 parts, xylol 1 part; complete differentiation in xylol, which should be applied and removed at least three times; when the section becomes fully cleared, mount in balsam. *Dehydration and differentiation with alcohol are not permissible.*

Termination.—Discharge may occur as in pseudomembranous formation. (See Pseudomembranous Inflammation of Mucous Membranes.) Liquefaction, absorption, retention, and suppuration not uncommonly occur. More or less absorption, followed by repair, is not infrequent. As in liquefaction necrosis, regeneration of the destroyed tissue is rare. On the surface of the mucous membranes, however, the destroyed cellular elements are not infrequently regenerated.

Site.—Wherever embolism may occur, and in all forms of capillary stasis; it occurs on epithelial surfaces and in glands made up largely of epithelium, such as the liver; the same condition has been observed in the connective tissues, muscles, and fat.

3. Fat Necrosis.—Whether this deserves a distinct position among the necroses is not fully determined. It is most constantly associated with hemorrhagic pancreatitis, in which condition it occurs in the pancreas, peripancreatic fat, and in the fat of the abdominal wall. It has been found in other conditions, and with no discoverable lesion of the pancreas. The areas of fat necrosis vary in size from one or two millimeters to five centimeters, are usually spheroid or ovoid in outline, are white, and resemble, in a way, disseminated neoplasms or tubercles. In time they may be infiltrated by lime salts; this infiltration is further explained if we accept the statement of Langerhans that the necrotic areas consist of a combination of the fatty acids with lime salts. Sometimes areas are softened, but later, as a result of the calcific matter present, they may be gritty. The exact cause of the process is unknown. The presence of steapsin, the fat ferment of the pancreas, has led to the belief that the presence of this body is the determining factor. Some hold that the process depends upon bacteria or bacterial products, while others believe that it is brought about by trophic influences. Recent clinical and experimental evidence would seem to indicate that the change in the fat was brought about through the activity of the pancreatic ferment.

4. Cheesy necrosis, or **caseation,** frequently begins as a coagulation or liquefaction necrosis, followed by a fatty degeneration of the cellular elements and the conversion of the mass into a liquid or semifluid material resembling cheese. The fluid is

taken up by the lymphatics, in some cases giving rise to *dry caseation*, such as is seen in old tubercular abscesses in which the fluid has been absorbed, leaving nothing but the cellular detritus. Caseation is not always dependent upon the removal of the fluids and the retention of the cellular detritus, as is shown by the fact that many caseous areas undergo no diminution in size at any period in their evolution. This is partly explained by the occurrence of cell migration into the necrotic area, the newly arriving

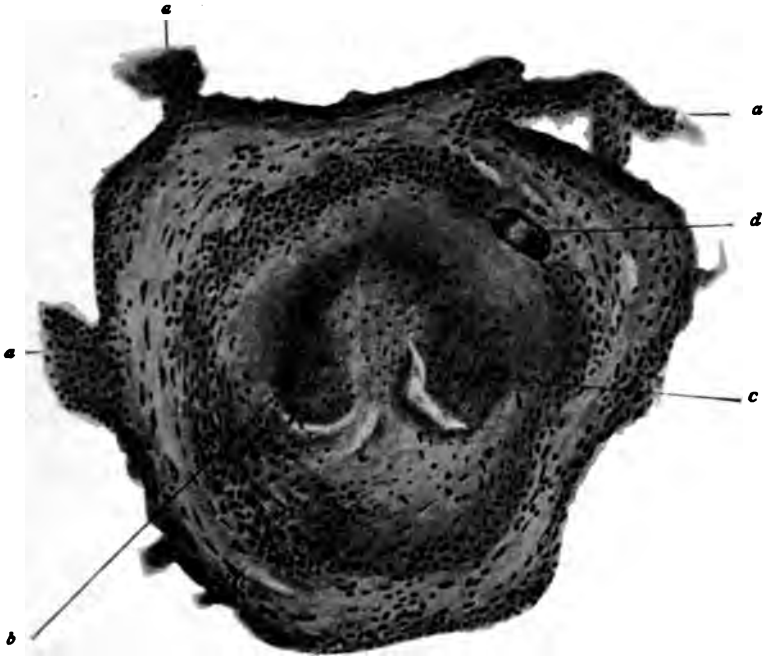

FIG. 184.—CONFLUENCE OF TWO TUBERCLES. SECTION OF LUNG.

Hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. The mass has originated in the vesicular wall, parts of which can be seen at *a*, *a*, *a*, running off to surround adjacent air vesicles; *b* and *c* have been two distinct tubercles, which are now beginning to show caseation. Around the caseous area is a zone of lymphoid cells in which, at *d*, is a solitary giant cell. Such eccentrically placed giant cells are not infrequent. The vesicular walls, which leave the tubercle mass at *a*, *a*, *a*, show considerable thickening (⅙-inch objective, ½-inch ocular).

cells themselves undergoing necrosis and their solid constituents remaining. The entrance of cells and fluids, as well as the absorption of the latter, account for the nodules retaining approximately their original size. In addition to the detritus arising from disintegration of the normal elements present and the necrotic cells, caseous nodules may contain bacteria. The or-

ganism most frequently present is the tubercle bacillus, which may be at times demonstrated in caseous nodules that are evidently old. Recently formed caseous areas are not uncommonly surrounded by a zone of inflammation. Older nodules may, from causes not well understood, show recrudescence of the original process.

Causes.—The process arises almost exclusively in connection with tuberculosis, but is occasionally seen in other chronic infections; in some instances small nontubercular abscesses may caseate. Caseation is sometimes seen in serous cavities: *e. g.*, pericardium or pleura. Rarely, the retention of mucoid materials, as in the Fallopian tubes, may be followed by inspissation and caseation.

Results.—Once the caseous mass is thoroughly encapsulated, it becomes permanent; the capsule is likely to become calcareous, and lime salts may be infiltrated into the cheesy material, converting it into a stone-like structure. The condition can not be properly said to be a cure, but only a quiescent stage, likely at any time to be followed by recrudescence of the original exciting cause.

5. Sphacelation en masse, or Gangrene.—This process is also known as *mortification*. A surgical term, *necrosis*, is applied to death of bone *en masse*. Gangrene or mortification is the death of any tissue, followed by putrefaction, while attached to the living body.

Varieties.—(*a*) *Moist gangrene*, which is further divided into (*1*) *circumscribed* and (*2*) *spreading*; (*b*) *dry gangrene*; (*c*) *hospital gangrene*.

(*a*) **Moist gangrene** may arise from disturbance of the blood supply—arrest of arterial influx, capillary flow, or venous exit. Gangrene may result from edema; when due to injury, it is known as *traumatic gangrene*; when caused by inflammation, it is called *inflammatory gangrene*. The inflammatory processes arresting capillary circulation, coagulation necrosis occurs, followed by gangrene. The cutting-off of the blood supply may result from occlusion of the artery by an embolus or thrombus, or a similar obstruction of a vein. Continuous pressure upon an area by progressive lessening of the blood supply leads to softening, and is followed by infection giving rise to gangrene. Destruction of tissue vitality by injury, whether traumatic, chemic, or thermic, leads to gangrene if putrefaction occur.

Gangrene in all its forms represents death of the tissue involved, plus infection. Without infection mummification, or drying without putrefaction, would occur. Such a condition is rarely,

if ever, seen. The odor of dry gangrene is significant of infection. In *spreading gangrene* a violent infection occurs, spreading by the lymphatics, and with such rapidity as to preclude arrest by the resources of the tissues involved. The infectious processes associated with gangrene are not fully understood. There is, however, a form of spreading gangrene—**malignant edema,** due to a bacillus—that has been thoroughly studied. (See Bacillus of Malignant Edema, p. 175.)

Noma, or **cancrum oris,** is a gangrenous process that attacks the mucosa of the mouth, lips, and adjacent structures. (See Diseases of the Alimentary Canal, part III.) A similar if not identical process has been observed in the external genitals, particularly in the female. In a number of these cases the diphtheria bacillus has been found.

Symmetric gangrene—Raynaud's disease, or **digitu mortui**—is a form of gangrene assumed to be due to arteriovascular spasm. It most commonly involves the same fingers on both hands, and is associated with or preceded by nervous or neuralgic phenomena that indicate its association with the nerves—sensory and, probably, trophic.

Morbid Anatomy of Gangrene.—The tissues involved become soft, pulp-like, with liquefaction of the fat and cellular elements; as this proceeds blebs form upon the surface and discoloration occurs—reddish-purple, then black, with varying shades of green. Putrefactive bacteria gain ingress and give rise to the chemic phenomena of putrefaction. Gases may be produced, and these, infiltrating the gangrenous tissue, give rise to *gangrenous emphysema;* the blood pigment breaks down and discolors the fluids, which may be extruded through the skin. The gases of putrefaction give rise to the horribly fetid odor at times present. Where the gangrenous mass joins the living tissue, a line of demarcation occurs; this line represents the point at which the tissue is viable, and where tissue death and the processes of infection are arrested, although the chemic agents engendered below this point may be absorbed. At this line of demarcation embryonic tissue, followed by granulation tissue, develops; these, progressing from the surface, separate the dead from the living tissues; in the soft parts this progresses with considerable rapidity, while in bone the process is much slower. In the dead tissue putrefaction proceeds exactly as it would if the tissue were separate from the body; advanced fatty changes occur in the cells, which eventually liquefy. The gases produced are compounds of hydrogen, sulphur, ammonium, etc.

During the destructive metabolism of tissue, induced and car-

ried on by bacteria, in addition to the products already mentioned are certain chemic bodies always the essential result of microbic growth—ptomains. These, for the most part, are highly diffusible, and are rapidly absorbed by the living tissues, and, entering the circulation, give rise to the systemic symptoms of gangrene. As well known clinically, we can understand, pathologically, how the intensity of the symptoms depends upon the amount of poison generated in the gangrenous focus, the rapidity of its absorption, and the resistance of the patient.

In *spreading gangrene* the infection promises to be rapidly fatal by its quick spread and the extreme activity of the noxious agents absorbed; hence, the surgeon lays great stress upon the necessity of immediate removal of the invading element. The urgency of the case is augmented by the fact that no line of demarcation occurs. In circumscribed gangrene the bacteria present may not be able to invade the adjacent normal tissues possessing their usual degree of resistance. In spreading gangrene, however, the evidence would seem to indicate that the tissue resistance must be reduced or that the bacteria possess the power of infiltrating and destroying tissue not previously injured. By some, spreading gangrene is believed to be an infection of the lymph-spaces, along which the bacteria travel, elaborating their poisons, which, in turn, destroy the adjacent tissue.

(*b*) **Dry gangrene** differs from the preceding in that the less juicy nature of the tissues involved resists infection and shows a more marked tendency to mummification. It commonly results from atheroma or obliterative changes in the blood-vessels to the part. The skin being unbroken, there is little tendency toward infection and consequent putrefaction. It is associated occasionally with diabetes and other adynamic states in elderly people having the vascular lesions already noted. It is spoken of as *senile gangrene* and as *diabetic gangrene* under the conditions just named.

(*c*) **Hospital gangrene** is now a historic disease, modern antisepsis having led to its disappearance. It probably represented an infection the exact nature of which we can only surmise.

CHAPTER V.

CIRCULATORY DISTURBANCES.

Anemia.—The term anemia is used to designate certain changes in the blood in which its functional activity is lessened; but, as here considered, reference is made to the **local anemia** dependent upon changes in the circulatory apparatus, and not, essentially, upon changes in the blood itself; it is, therefore, an **ischemia.**

Causes.—(1) Faulty distribution of the blood, as in shock, when the blood tends to accumulate in the larger veins, particularly the splanchnic veins. (2) A very much weakened circulation, whether due to shock, disease, or the influence of poisons, may be too feeble to force the blood through the capillary system, particularly in the skin and brain; hence, cerebral anemia and cutaneous anemia may arise. (3) Diseases of the blood-vessels, such as atheroma; obliterating inflammation of an artery will lead to lessened blood supply in the distribution of that vessel. (4) Pressure. (5) Occlusion of an artery, whether complete or partial, as by ligature, pressure of a tumor, thrombosis, or embolism. (6) Spasm of the blood-vessel, due to contraction of its muscle fibers, either dependent upon or independent of the innervation. (7) An abnormal perivascular pressure in the area involved may lessen the possible ingress of blood. This increased perivascular pressure may arise in a number of ways. Organizing cicatricial tissue may, by its contraction, so increase the pressure normally exerted upon the capillaries that the blood flow may be greatly diminished or even obliterated in some, if not all, of the capillaries of the area involved.

Morbid Anatomy.—The area is pale and bloodless, and the temperature is likely to be lower than normal, or, when the general body-temperature is above the normal, the anemic area will show a less marked elevation; there may be some edema, and, as will be seen later, the stagnation of regurgitation may be evident.

Effect.—If the ischemia be temporary, there will be but slight interference with function; if the process be slowly developed, a gradual lessening of function will occur, and the area may undergo degenerative, necrotic, or atrophic changes; the same result may follow a slight anemia that persists. If the local

anemia be suddenly developed, and the blood supply is insufficient to maintain nutrition, death of the part may ensue; such a condition may follow ligation of the main artery of a limb. Local anemia lessens the functional activity of the tissues involved, diminishes their reparative power and resistance to infection, and if the flow be greatly reduced or abolished, even for a short time, degenerative changes take place in the capillary walls which increase their permeability and favor the formation of exudates, and sometimes capillary hemorrhages, upon the reentrance of blood or the reestablishment of the circulation, or after the occurrence of satisfactory collateral anastomosis.

If the cutting-off of the blood supply occur in an artery supplied by a branch that communicates indirectly with the area involved, and the circulation be turned through the branch to supply nourishment in the indirect route indicated, such a process is spoken of as *collateral anastomosis*. With the occlusion of an artery the blood-pressure beyond the obstruction gradually lessens until a point is reached when it is less than the pressure in the veins. Backward distention may now occur, so that an area that at one time showed marked ischemia now becomes an area distended by venous blood. This constitutes *stagnation* or *regurgitation*, and probably ends in infarction. (See Embolism.)

Ischemia is sometimes said to be *collateral* or *compensatory* when it results from the accumulation of blood elsewhere.

Hyperemia (*"Active Hyperemia" or "Active Congestion" of Some Authors*).—This condition is dependent upon an increased arterial influx, a distention of the capillaries by arterial blood, and hence called *arterial hyperemia*, in contradistinction to a condition, to be considered later, in which the blood present is essentially venous.

Causes.—(1) Physiologic, as the hyperemia of the mucous membranes during digestion or of the uterine mucosa during menstruation. (2) In inflammation hyperemia constitutes the first stage, and usually persists during the activity of the processes. (3) Increased arterial pressure or tension; ordinarily, it is probable that the greater quantity of the blood is in the venous system, but when there is increased cardiac activity, the arterial and arteriocapillary systems become surcharged; examples of this are seen in the flushed face of active exercise and in the apoplexy that follows violent exertion. (4) *Neuroparalytic*, as when the stimulus to the vasoconstrictors is withdrawn. (5) *Neurotonic*, as when there is hyperactivity of the vasodilators. (6) Local anemia is, at times, quickly followed by a more or less marked arterial hyperemia. Thus, prolonged pressure is

not uncommonly followed by active hyperemia of the area. A similar hyperemia is seen to follow the removal of Esmarch's bandage, applied for the purpose of preventing hemorrhage during the progress of operations. The local anemia produced by cold is frequently followed by an arterial hyperemia. (7) A sudden stroke applied to the skin is quickly followed by the occurrence of a local hyperemia, probably depending upon a temporary paralysis of the vasoconstrictors. (8) Certain chemic bodies also induce hyperemia: *e. g.*, mustard, chloroform, cantharides, etc. These probably act by inducing inflammation,—in other words, as irritants,—and the result should therefore be considered with inflammatory hyperemia. Hyperemia is said to be *compensatory* and *collateral* when the blood is forced into one area by reason of its inability to enter another, or as the result of anemia elsewhere; such a condition is observed in the increased amount of blood sent to one lung when the other is solid or compressed.

Morbid Anatomy.—During life redness, increased cellular activity, and usually a slightly elevated temperature are manifest; swelling, discomfort, and, perhaps, pain may accompany the condition; if the process is physiologic, the functional activity is usually increased; in pathologic hyperemia inflammation is likely to occur. Persistent physiologic hyperemia may lead to hypertrophy; similar pathologic hyperemia may cause some of the degenerative processes already described. Postmortem, the evidence of hyperemia may be wanting, as the result of the emptying of the arteriole and capillary. Microscopically, however, there will usually be found capillary rhexis, and, if the process has persisted, degenerative or inflammatory changes may have ensued.

Plethora, also known as **polyemia** and **repletio,** implies an abnormal fullness of the entire vascular apparatus. Several forms have been described, dependent upon the material that is increased in the blood, whether it be an increase in the water, in the albuminous compounds, or in the corpuscular elements.

Thoma speaks of a **plethora vera,** in which the blood present is normal; **hydremic plethora,** as dependent upon an additional quantity of water; again, when the plethora seems to involve the entire vascular system, it is said to be **general plethora;** a localized form is described that is analogous to congestion, but is sometimes spoken of as **vascular plethora.** An overdistention of the lymph-spaces is spoken of as **lymphatic plethora,** a condition closely allied to edema. (See also chapter on the Blood, pt. III.)

Hemorrhage.—The escape of all the constituents of the blood constitutes what is ordinarily spoken of as a hemorrhage. Hemorrhages are said to be *arterial*, *venous*, *capillary*, or *mixed*,

depending upon the vessel or vessels from which the bleeding occurs. Hemorrhages as a result of solution in the continuity of the blood-vessels are spoken of as *hemorrhages per rhexin.* The hemorrhages that arise as a result of trauma are properly to be classified with this group. The injury to the vessel may not be sufficient to permit the escape of blood at once, but later degenerative or inflammatory change may cause the vessel to give way. Increased arterial tension is also said to be a cause of hemorrhage. It is probable, however, that the normal blood-vessel, whether it be artery, capillary, or vein, not previously injured or diseased, never ruptures as the result of a simple rise in the blood-pressure. Developing blood-vessels may form exceptions to this rule. When a hemorrhage occurs from a blood-vessel (capillary or vein) without manifest solution in the continuity of its wall, the condition is spoken of as *hemorrhage per diapedesin.* Such hemorrhage is seen to occur as a result of venous obstruction. The increased permeability of the blood-vessels is largely induced through interference with their nutrition, as after persistent local anemia, or as a result of injury, mechanical or thermic, as well as chemic; including under the last-named the destructive influences manifested upon the vascular endothelium by the poisons of many bacteria.

As illustrating the influences of bacteria and bacterial poisons in the production of capillary hemorrhage, the cutaneous, mucous, and submucous hemorrhages of septicemia, cholera, yellow fever, and allied diseases may be cited. There is a growing belief that rheumatism may be a bacterial disease, and, if so, the capillary hemorrhages present in the disease called purpura rheumatica may be of infectious origin. The extensive ecchymoses that occur in phosphorus-poisoning are probably brought about by alterations in the blood and by degenerative changes in the capillary walls. A similar explanation is probably operative with regard to the capillary hemorrhages induced by the poison of venomous reptiles.

In addition to the morbid conditions just considered,—in which it would appear that the occurrence of hemorrhage was dependent upon an acquired alteration in the blood or blood-vessel, or in both, and hence called an acquired hemorrhagic diathesis,—we occasionally find individuals possessing an extraordinary tendency toward the occurrence of severe hemorrhage resulting from the most trivial cause, which tendency seems to have been transmitted from ancestors who manifested the same peculiarity. Such a condition is called *inherited hemorrhagic diathesis*, or *hemophilia.* Hemophilia, or bleeding diathesis, is transmitted commonly from the mother; as a rule, the male children manifest the disease but

do not transmit it. The female children, on the other hand, usually show no manifestation of the habit, but transmit it to their children. No satisfactory explanation has been offered for this congenital hemorrhagic diathesis, although cases undoubtedly occur in which the hemorrhages are arrested by the application of agents favoring the coagulation of the blood.

When inflammatory, suppurative, infectious, or ulcerative processes approach the blood-vessel from without and destroy its walls, the consequent hemorrhage is spoken of as *hemorrhage by diabrodosis*, or *hemorrhage per diabrosin*. Such hemorrhages occur from blood-vessels in the cavities due to pulmonary tuberculosis and occasionally as a result of suppurative processes around the large vascular trunks of the neck.

The influence of the nervous system in the production of hemorrhage is but little understood. It may act indirectly through the vasomotor system, raising the arterial tension and increasing the pressure in diseased blood-vessels that are already taxed to withstand the normal blood-pressure, and hence, under the increased pressure, give way. Such action of the nervous system fails to explain hemorrhage from the stomach and intestines in diseases of the crura cerebri, and the occasional instances of vicarious menstruation manifested by hemorrhages from the nose, mouth, lungs, etc. The hemorrhages of hysteria would seem to be properly classed with this group.

Small areas of hemorrhage with sharply defined margins, at first red, then purplish, and eventually purplish-black, are known as *petechiæ*. *Purpuric hemorrhages* manifest themselves by numerous petechiæ situated in the submucous or subcutaneous structures; they are also occasionally observed under serous membranes. An *ecchymosis* is a submucous or subcutaneous hemorrhage, commonly due to injury, but also arising from other causes. Extensive infiltration of the connective tissues by blood is spoken of as *hemorrhagic infiltration*, or *bloody suffusion*, or *suggillation*. When blood collects so as to form a distinct tumor, it is called a *hematoma*.

Hemorrhages from various cavities and surfaces have received special names, depending upon their location or on the phenomena to which they give rise: hemorrhage from the nose is called *epistaxis;* hemorrhage from the lungs, *bronchopulmonary hemorrhage*, or *hemoptysis;* excessive menstrual flow is *menorrhagia*, and uterine hemorrhage occurring independently of the menstrual flow, *metrorrhagia;* hemorrhage from the bowels, *enterorrhagia;* hemorrhage of the urinary organs, *hematuria;* hemorrhage into joints, *hemarthron* or *hemarthros;* hemorrhage into the brain,

cerebral apoplexy, or *hæmatencephalon;* blood in the pleural cavity, *hæmathorax;* a collection of blood in the pelvic peritoneum or in the tunica vaginalis testis is spoken of as a *hæmatocele;* hemorrhage into the central canal of the spinal cord, *hæmatomyelia;* hemorrhage into the pericardium, *hæmopericardium;* hemorrhage into the peritoneum, *hæmoperitoneum;* and so on.

The *effects of hemorrhage* may be local or constitutional. The local changes to be considered are only those that arise in connection with accumulations of blood that remain in contact with the living tissues. Blood coming in contact with the digestive juices is more or less modified by their action. In the stomach it forms a brown or brownish-black, grumous substance, resembling coffee-ground; hence the term "coffee-ground vomit," used to designate the vomiting of more or less altered blood. Within the intestinal canal the alteration is more marked when hemorrhages have occurred sufficiently high to permit prolonged contact with the intestinal juices. The blood of rectal hemorrhage may escape with but little alteration. In hemorrhages arising in the upper intestine the blood is usually converted into a tarry substance. Blood thrown out into the serous cavities may be absorbed.

The fate of hemorrhages into the connective tissues is largely dependent upon the amount of blood extravasated and upon the damage to which the tissue has been subjected. In small hemorrhages the blood rapidly breaks down, the red corpuscles yield their hemoglobin and undergo fragmentation, and eventually solution, the resulting products being carried away by the lymphatics. The display of color that occurs in bruised areas or areas of local hemorrhage is dependent upon alterations in the hemoglobin. Distinct collections of blood (*hæmatomata*), if still communicating with an artery, may remain as false aneurysms. (See Aneurysms.) The small amount of infiltration at the periphery of the tumor is replaced by cicatricial tissue, which, with the condensed structures, forms a false wall; this false wall may limit the hemic tumor or may gradually yield and eventually rupture. Similar collections, not communicating with an artery, usually, in time, undergo complete absorption; sometimes, however, they are walled off by a newly formed connective-tissue membrane, which may become calcareous; in time, this may contract and eventually leave nothing but an area of induration. Small residual collections of unabsorbed blood may undergo calcareous change.

The *systemic phenomena induced by hemorrhage* are dependent upon the amount of blood lost and upon the rapidity with which

it escapes. A considerable quantity of blood may be lost by a slowly oozing hemorrhage without giving rise to any conspicuous symptom. A much smaller quantity, however, suddenly ejected by an artery, may induce a rapidly fatal issue. In severe hemorrhage the blood-pressure begins to fall coincident with the blood loss. This fall in blood-pressure lessens the amount of blood that will escape (in the same length of time under higher blood-pressure the loss would be greater), and favors the occurrence of coagulation, at the same time permitting contraction of the blood-vessel. The sudden drop in blood-pressure, with the associated faulty distribution of the blood, give rise to cerebral anemia, which, if the fall be marked or long continued, may terminate fatally. Under lower blood-pressure a clot not uncommonly forms in the wounded vessel, and with the complete arrest of hemorrhage the volume of blood is made up as soon as possible by removal from the lymph-spaces of the available fluid in the body, gradually restoring the circulatory volume and paving the way to complete regeneration of the blood. (See Blood.)

Congestion.—Congestion is also known as *venous hyperemia* or *venous congestion*, *passive hyperemia* or *passive congestion*. This condition is due to faulty exit of the blood, and to its accumulation in the veins and capillary system of the area involved. In contrast to hyperemia, in which there is an increased amount of arterial blood, in congestion there is an increased amount of venous blood.

Causes.—Any condition that prevents free venous exit, and that at the same time does not limit arterial ingress; pressure, and constricting bands that compress the easily collapsed veins and not the more rigid arteries; diseases of the veins, such as inflammation and thrombosis; tumors, and pressure from surrounding or adjacent organs or structures; in a feeble circulation congestion is favored by gravity, as in the congested extremities of individuals suffering from valvular heart-disease; this congestion, dependent upon feebleness of the circulation, is illustrated in the **hypostatic congestion** of the lungs that accompanies typhoid fever and other adynamic states; here the congestion is favored by gravity, as already noted. Arrest of arterial flow may lead indirectly to congestion depending upon the regurgitation of blood from veins in which a more or less constant pressure is maintained; such vascular distention, at first manifested in the larger veins, but sooner or later reaching the venules and capillaries, is termed the *congestion of regurgitation*.

Morbid Anatomy.—This is largely dependent upon the duration of the process and its magnitude. During life the area involved is

edematous, swollen, bluish, with a temperature usually lower than normal. The cause of the swelling will be further considered when dealing with edema. The gradual reduction in circulatory activity gives rise to overdistention of the capillaries of the area involved, degenerative changes in their walls, diapedesis, and corpuscular plugging. The distention of the capillaries by plugs in which the cellular elements may no longer be recognized (stasis) is frequently seen. As a result of the breaking down of these quiescent red blood-cells, both within and without the blood-vessels, a certain amount of pigmentation may be present, particularly where the process has been long continued. Prior to complete stagnation and dissolution of the cellular elements restoration of the circulation is possible. The process is likely to terminate in degenerative, atrophic, or necrotic changes in the tissues involved; this is due to the fact that nutrition in any given area is as dependent upon the removal of the products of cell life as it is upon the supply of pabulum. If the area involved be large, and the process be sufficiently marked, coagulation necrosis, followed by gangrene, may occur. Such extensive necrotic processes are, of necessity, preceded by stasis. Congestion is likely to persist postmortem and to be evident, thereby differing from hyperemia. The form of congestion that develops after the cessation of circulation, known as *suggillation*, must be differentiated from congestion that develops during life. Postmortem suggillation is not usually accompanied by edema, and does not show the nutritive changes that accompany antemortem venous stasis. (See p. 22.)

Stasis.—When, as the result of the slowing of the circulation, the obstruction of gravity, inflammation, or of injury, the blood stops circulating in the capillaries of an area, the condition is spoken of as stasis. It is a very common sequence of congestion, occasionally occurs in hyperemia, and is a more or less constant phenomenon in inflammation. The extent of stasis in inflammatory processes is dependent upon the activity of the inflammation and upon the recuperative powers of the circulation. The virulence of the infection is no doubt also a determining factor. In addition to the causes just mentioned, stasis occasionally arises as a result of tension occluding the blood-vessels to or from an area, and may also be caused by inspissation: as, for example, from prolonged exposure of serous surfaces, notably the peritoneum. The corpuscular changes terminate in dissolution, fragmentation of the cells, and not infrequently necrosis of the capillary walls; the necrotic change may also involve the perivascular structures.

Edema implies abnormal or excessive transudation of the fluid portion of the blood into, or its abnormal retention in, the lymph-

spaces. As the large serous cavities are generally conceded to be lymph-spaces, the accumulation of serum such as is seen in the ascites that may accompany cirrhosis of the liver belongs truly to the edematous condition.

Causes.—The pathology of edema is intimately associated with the normal process of lymph formation. When physiologists satisfactorily determine the origin of lymph, we will be better able to appreciate the overdistention of the lymph-spaces seen in edema. It is probable that the cause of edema is never a single factor, usually depending upon a combination of conditions, among which may be considered alterations in the blood, in the blood-pressure, and in the capillary wall, and interferences with the normal flow of lymph. To these may possibly be added decreased perivascular pressure, and possibly chemic and structural changes in the tissues; that the nervous system may exert a certain causative influence can not be overlooked, but what the factor is or the manner of its action can not be so accurately determined. Some are inclined to believe that mere changes in the blood will not produce edema until sufficient time has elapsed for the blood changes to give rise, either directly or indirectly, to changes in the vessel walls. The changes in the vessel walls consist, for the most part, of alterations in the endothelium of the capillaries. The endothelium may become granular, cloudy, or even partially exfoliated. With such alterations in the endothelium, enlargement of the stomata occurs, or even separation of the endothelial plates along their line of juncture. It is probable that in all forms of edema that arise from increased blood-pressure some change in the endothelium is an essential part of the process. When there is an obstruction to the onward flow of the blood, such as may occur from ligation or occlusion of the principal veins, or when there is backing of the blood, which increases the pressure in the capillaries and leads to such degenerative changes in the endothelium as to permit extravasation of the serum, edema occurs. Similarly, venous congestion, due to inability of the heart to propel the venous blood, may induce the same lesion. That edema produced by obstruction to the onward flow of the blood is directly due to the increased intracapillary pressure can not be said to be definitely demonstrated. It is probable that it arises, in part at least, as a result of associated degenerative changes in the endothelium, increasing the permeability of the vascular wall and permitting the occurrence of serous transudation. The fact that the blood-vessels in an edematous area may show no recognizable structural lesion has led to the belief that edema may, under certain circumstances, be dependent upon an

increased secretory action of these cells, presuming, of course, that the normal lymph is produced by a process of secretion and not simply by transudation. The presence of certain materials in the circulation undoubtedly favors the occurrence of edema. For the most part these are toxic substances, of which certain bacterial poisons may be taken as examples. It is not improbable that they increase the diffusibility of the serum and at the same time injure the endothelial cells. The edemas that occur in the last stages of tuberculosis and in various cachexiæ associated with lowered nutrition, are probably dependent upon the faulty nourishment of the vascular endothelium as well as upon alterations in the blood, and in not a few of these the presence of toxic materials in the circulating fluids can not be positively excluded as adjuvant factors. The influence of tissue tension in the occurrence of edema must not be overlooked. With vascular changes practically the same, edema must, of necessity, occur with more rapidity in lax tissues, such as the eyelid and scrotum, than in tissues of greater density, such as periosteum and bone. Normally, the nutrition of the tissues is maintained, in part at least, by serum passing out from the vessels into the perivascular structures (primitive lymph-spaces); the cells abstract from this fluid the elements necessary for their nutrition, and yield to it excrementitious products, after which it is removed from the tissues by the lymph-stream. It will be seen that any obstruction to the onward flow of the lymph, such as may result from pressure upon the lymph-duct, may give rise to an accumulative edema in the area drained without the necessity of presupposing any degenerative change in the blood-vessels of the part.

A form of edema known as **edema ex vacuo** is said to occur when brain-tissue or tissue from the spinal cord disappears by any process, and the resulting cavity, or loss of tissue, or shrinking of the organ, must be filled in.

Edema is often named for the cause that gives rise to the lesion in the blood-vessel or blood primarily. Such edema may be known as *toxic*, *infectious*, *cachectic*, *traumatic*, *ischemic*, *inflammatory*, *thermal*, or, in some cases (as when the dilatation of the blood-vessels is dependent upon errors or lesions in innervation), the condition may be spoken of as *trophic edema* or *neuropathic edema*.

Morbid Anatomy.—Edematous tissue is usually pale, pits on pressure, and, as a result of the deficient circulation of the blood, is lower in temperature than the normal. On incising, serum escapes, and the watery condition of the tissue can be readily seen. By reason of the deficient circulation, the resist-

ance of such tissue is lowered, and this renders it extremely susceptible to infectious and necrotic processes. Not uncommonly the edematous tissue shows well-marked and advanced degenerative changes. (See Hydropic Degeneration, p. 244.) Edema fluids, spoken of as *transudates*, differ materially from inflammatory accumulations, called *exudates*. Edema fluids possess a low specific gravity, are poor in cells, and contain a relatively small proportion of albumin. A specific gravity of 1016 to 1020 is not uncommon in inflammatory exudates, while dropsical collections rarely attain a specific gravity of 1010, usually falling below —1006 to 1008. Transudates are commonly clear; exudates are turbid and usually rich in leukocytes.

Different names have been given to the accumulations of dropsical fluids, based upon the location, cause, or admixture with other fluids. When the edema is more or less general, the term *hydrops universalis* is applied; edema of the connective tissues, particularly of subcutaneous connective tissues, is called *anasarca;* dropsy of the peritoneum is spoken of as *hydroperitoneum* or *ascites;* dropsy of the pleura, as *hydrothorax*, which condition may be unilateral or bilateral; dropsy of the pericardium, as *hydropericardium;* fluid accumulation in joints, as *dropsy of the joints* or *hydrops articuli;* etc. The origin of edematous collections is sometimes indicated by the name: as, for example, renal dropsy, cardiac dropsy, congestive dropsy, angiosclerotic edema (edema associated with sclerotic changes in the blood-vessels). Reference has already been made to toxic and infectious edema and other forms of edema.

THROMBOSIS.

A **thrombus** is a more or less uniformly solid or a semi-solid body, formed during life in the heart or blood-vessels, and resulting from causes that lead to the agmination, agglutination, or coagulation of one or more elements present in the blood. The older definition—an antemortem intravascular clot—did not take into consideration the agmination and agglutination of platelets and leukocytes. Most thrombi, however, are nothing more than fibrinous coagula, relatively rich in leukocytes and platelets. The term **thrombosis** is applied to the process terminating in the formation of a thrombus. It is also somewhat loosely used to cover the associated conditions.

In most instances there is little difficulty in differentiating thrombi from postmortem clots. Coagula formed after death have certain points that are highly characteristic; they are usu-

ally smooth on the surface, and show no attachment to the vessels in which they lie, although they may be entangled: as, for example, in the muscular columns or the tendinous cords in the heart. This absence of attachment is highly important, even when a thrombus has been dislodged from its point of attachment; the point from which the thrombus has been detached will usually be easily recognized as a roughened area upon the blood-vessel or heart wall, a cardiac orifice or valve leaflet. In many instances a point can be found on the thrombus that shows evidence of past attachment. The postmortem clot has a moist, glistening surface, is usually red in color; some part of it always shows the redness due to red blood-cells, and an important differentiation, for which we are indebted to Cohnheim, is that in the thrombus there is little difficulty in longitudinal splitting. The thrombus usually has a frayed-out end. A postmortem clot does not show the changes that may be seen proceeding in a thrombus. (See p. 271.)

Occasionally, where coagulation of the blood postmortem goes on very slowly, sufficient time elapses for the red blood-cells to settle to the most dependent portion, giving rise to a clot the upper layers of which are colorless and jelly-like, while the lower portion shows a deeper color than usual by reason of its containing more red blood-cells.

Very often, when life is almost extinct (agonal period), the very slow rate at which the blood is flowing may favor the occurrence of thrombi, which, later, become continuous with postmortem clots, coagulation going on around the thrombus after death. While not restricted to the right side of the heart and the pulmonary artery, such clots frequently occur in that location.

Red thrombi contain blood coloring-matter usually in the entangled red blood-cells; these are the thrombi that form in stagnant or practically quiescent blood. **White thrombi** are thrombi consisting of fibrin with a varying number of leukocytes and blood platelets, and are formed in flowing blood. Thrombi may be mixed—the so-called **gray thrombi,** in which the gradual slowing of the blood has led to a slight deposition of the red blood-cells with the fibrin. As a result of ribbed, "frayed-out," or irregular thrombus-formation, longitudinal cavities are sometimes formed in which the more or less quiescent blood proceeds to clotting, and enters into the formation of the completed thrombus. This condition gives rise to thrombi that may be, in a sense, mixed, certain parts of the thrombi being distinctly red, other parts gray, and still other areas red and jelly-like, closely

resembling the thrombi formed in quiescent blood. When the thrombus is made up of layers, such as occur in the cavity of an aneurysm, the thrombus is said to be **stratified.** When a thrombus remains where it originated, and arises independent of other thrombi, it is called a **primary thrombus.** The term **propagated thrombus** is applied to a thrombus that extends some distance from the point at which it originated; such thrombi are extremely likely to show different ages at different points, and may extend to an indefinite length. A thrombus developing from an embolus, or a thrombus that arises secondary to an existing thrombus, is known as a **secondary thrombus.** When a thrombus leads to occlusion of the blood-vessel in which it lies, it is said to be an **obstructing thrombus.** When it permits the blood to flow one way and occludes a current flowing in the opposite direction, it is termed a **valve thrombus.** When the thrombus lines the wall of the cavity,—*e. g.*, an aneurysm or a blood-vessel,—it is said to be a **parietal** or a **mural thrombus.** When a thrombus extends around a blood-vessel, it is said to be **annular.** When a thrombus has formed with a distinct canal, it is spoken of as a **channeled** or **canalized thrombus.** The "*ball thrombus*" is not attached, although evidence of recent attachment may be present either on the thrombus or on the vascular or cardiac wall; a point of separation from a fragment, still attached, may often be recognized. Ball thrombi are most frequently found in the dilated left auricle in cases of mitral stenosis. Polypoid or pedunculated thrombi, so-called *cardiac polypi*, are most frequently seen in the left auricle; the point of attachment is usually the margin of the fossa ovalis or its immediate vicinity. The pedicle, and not uncommonly a larger part of the thrombus, may show advanced organization. The structure of such partly organized polypi may resemble fibrous or myxomatous tissue, and hence they have been termed *fibromatous* and *myxomatous polypi* respectively. An endothelial covering is sometimes demonstrable, and calcareous infiltration may be in progress or even in an advanced stage.

The most important division of thrombi is into **simple** or **bland** and **infected** or **infective,** the former meaning aseptic thrombi, containing no bacteria, the second meaning thrombi containing bacteria, hence *infected thrombi.* A further division of infected thrombi has been proposed. It is suggested that the term septic thrombi be applied to those containing organisms of suppuration, and the term putrid thrombi to those that contain bacteria of decomposition. The fact that the bacteria of decomposition may be present alone or associated with the organisms

of suppuration deprives such a division of much of its theoretic value.

Thrombi are sometimes called **arterial** or **venous,** and, under the latter, a separate form is named, dependent upon its location in a distinct venous system—**portal thrombi.**

Causes.—The essential exciting cause of a thrombus is that process terminating in coagulation of the blood. Other causes are: (1) Any body within the circulation, not covered by endothelium, will lead to attachment of the third corpuscle and to the subsequent formation of a clot or thrombus; (2) roughening of the vascular wall, as observed in atheroma; (3) slowing of the circulation, such as occurs in partial occlusion of a blood-vessel, or in complete occlusion, as represented by ligation. It is maintained, and probably justly, that a blood-vessel may be ligated and its lumen occluded without the intervention of a clot. This implies great care in applying a ligature, so that it does not injure the endothelium. When a blood-vessel is ligated in its continuity, two thrombi are usually formed: one on the cardiac side, known as the **proximal thrombus,** and a second in the blood-vessel, beyond the point of ligation, known as the **distal thrombus.** It is probable that complete or partial obstruction gives rise to changes in the endothelium of the vessel wall, and this favors the mural lodgment of leukocytes and third corpuscles, and hence of a thrombus. As will be noted later, the formation of a thrombus is not essential to the obliteration of a blood-vessel in which the circulation has ceased. Indeed, it is held by some authors that thrombosis interferes with the obliterative endarteritis that normally leads to the disappearance of a blood-vessel. (4) Any alteration in the vessel wall that injures the endothelium favors the development of a thrombus. (5) Chemic changes in the blood also favor the development of thrombi; examples of these are seen in diphtheria and in adynamic conditions with very much slowed and enfeebled circulation. Such thrombi are called **marasmic thrombi.** (6) Hyperinosis, such as develops in pregnancy, is nature's method of anticipating hemorrhage, the increased amount of fibrin favoring the arrest of bleeding by the development of thrombi. Hyperinosis is not of itself an exciting cause of thrombosis, as many conditions are associated with an increase in the amount of fibrin-forming elements in the blood without any marked tendency toward the occurrence of thrombosis. (7) Chemic changes leading to a thrombus may be produced in the blood by the injection of certain agents: *e. g.*, ether. (8) Where a tumor infiltrates or comes in contact with a blood-vessel, a thrombus is likely to form. (9) A primary

thrombus favors the development of secondary thrombi. (10) Mycoses of the blood favor the development of thrombi. (11) Embolism favors thrombus-formation.

Changes That a Thrombus May Undergo.—These changes are dependent upon whether the thrombus is *simple* or *infective*.

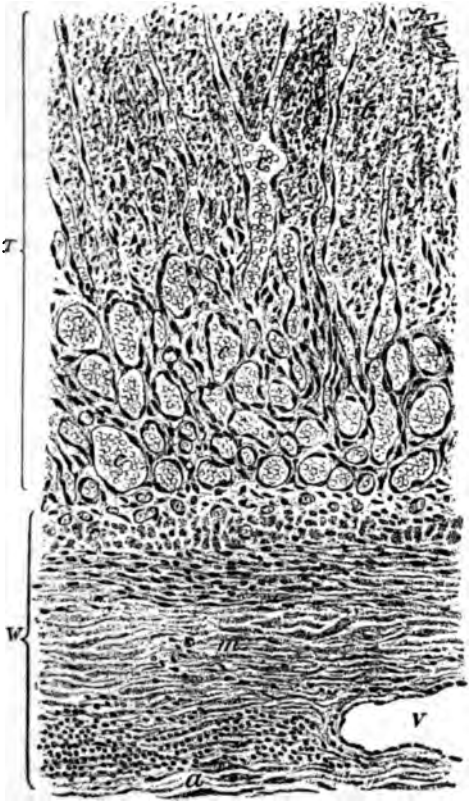

FIG. 185.—SECTION THROUGH A PART OF A VEIN WITH ITS CONTAINED ORGANIZING THROMBUS.—(*Schmaus.*)

W. Wall of vein. *a.* Adventitia. *m.* Media. *i.* Intima. *V.* Blood-vessel in the wall of the vein. *T.* Thrombus, now largely composed of granulation tissue. *c, c, c.* Young blood-vessels; those near the intima are larger and more fully developed than those extending into the thrombus, the latter being younger.

In **infective thrombi** the only changes that are likely to occur are those constantly associated with infection: namely, *liquefaction, softening*, or *breaking down;* rarely, in infected thrombi, dislodgment may occur. The changes to be considered in *simple thrombi* seldom occur in the infected thrombi, with the exception

of softening. The fragments of an infected thrombus become infected emboli, and lead to the dissemination of the infective material and to its deposition in other parts of the organism; besides this, infected thrombi are constantly throwing into the circulation bacteria or the products of bacterial life, this condition constituting what is known as *septicæmia* or *mycosis* of the blood. When the infected material contains pyogenic organisms, the emboli, lodging, give rise to abscesses; such abscesses are spoken of as *pyæmic* or *metastatic*, and the disease is known as *pyæmia*. Before the elucidation of the subject of blood-poisoning, afforded by our knowledge of bacteria and infectious processes, it was presumed that metastatic abscesses resulted from the presence of pus in the blood; hence the name *pyæmia*. We now know that the condition is due not of necessity to the presence of formed pus, but to that of agents capable of inducing suppurative processes. The following changes may occur in thrombi:

1. Dislodgment.—This occurs but rarely. The cases that the writer has observed have been from large tumors of the uterus, where a thrombus has formed in one of the massive sinuses of such a tumor, and, becoming dislodged, has reached the lung and blocked the larger vessels to that organ, leading to almost instant death. Dislodgment of a thrombus is favored by any sudden increase in the rapidity of the circulation, particularly when the accelerated current is brought directly in contact with the thrombus; manipulation of the affected part, or even comparatively slight muscular movement in the affected limb, when an extremity is involved, may give rise to dislodgment.

2. Decolorization.—Decolorization is possible only in the red thrombus, and is due to the gradual absorption of the coloring-matter by the circulating blood, which flows over, around, or through it.

3. Re-solution.—It is difficult, if not quite impossible, to demonstrate the occurrence of this process; but there can be no doubt that the simple, noninfected thrombus, due to temporary conditions, may be dissolved or may undergo solution upon the removal of the cause.

4. Softening.—This is not so common in the simple as in the infected thrombus, and is usually due to conditions of development, to the location and size of the thrombus, and to blood changes that militate against the process of organization. When this change occurs without infection, it is termed ***simple softening;*** when bacteria are present, *septic* or ***infective softening.*** When softening and breaking down occur, the fragments, reaching the circulation, form *simple* or *infective emboli*, depending on whether

the thrombus contained viable organisms or not; more commonly, instead of softening, there is really a condition of *fragmentation*, in which merely the end of a thrombus is broken off.

5. Organization.—This process is possible only in the absence of infection. It may occur in infected thrombi after the subsidence of infection, although upon this point there must remain much doubt. The conversion of the thrombus into connective tissue is effected largely through the activity of the endothelial cells of the intima. Before the beginning of organization considerable contraction is usually brought about by removal of the fluids present in the thrombus, and possibly by a certain amount of liquefaction and absorption. Where the thrombus becomes continuous with

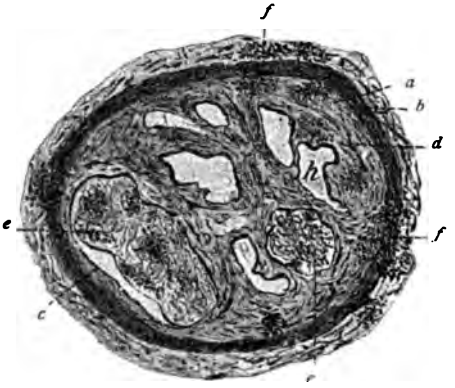

FIG. 186.—TRANSVERSE SECTION OF A THROMBOSED BLOOD-VESSEL IN WHICH ORGANIZATION AND CANALIZATION OF THE THROMBUS ARE IN PROGRESS.

a. Newly formed connective tissue of the thrombus. *b*. Tunica media. *c*. Tunica intima. *d*. Young cell infiltrate of the thrombus. A similar infiltrate of the coats of the vessel is shown at *f*, *f*. *e*, *e*. Remainder of the not yet organized thrombus. *h*. Developing canals.

the intima, the endothelium gradually extends over its surface. From this endothelial covering processes of young connective-tissue cells extend downward into the thrombus, forming capillaries. A similar proliferation of the endothelium beneath the thrombus also takes place, and young blood-vessels from the adjacent nutrient vessels are pushed forward into the proliferate. During the extension of this embryonic tissue formation further absorption and shrinkage of the thrombus occur. Gradually the new connective tissue replaces the thrombus, and organization of the cicatricial tissue is completed as usual. (See Process of Repair.) The activity of the leukocytes in this process is no longer conceded to be important. With the presence of infection large numbers of leukocytes may be found. They are not, however,

regarded as essential elements in the production of the embryonic tissue through which organization is eventually completed. The influence of the organized body upon the blood-vessel will be, of course, dependent upon the extent and location of the thrombus and upon the completeness with which it occludes the vascular lumen. The influence of the subsequent cicatricial contraction is shown by the deformity that it induces, and is particularly marked in the organized thrombi that constitute the vegetations on the valve leaflets in endocarditis. (See Results of Endocarditis.)

6. Calcification.—When a thrombus forms in a slowed circulation,—*e. g.*, of a dilated vein,—and is attached to the vein or lodged in the sinus of the valve, infiltration by lime salts not uncommonly occurs, and produces the so-called *phleboliths*, or "*vein stones*"; arterioliths and stone-like concretions attached to the cardiac walls or orifices are produced in a similar manner; infiltration of lime salts is also likely to occur in a thrombus that is organizing or that has organized.

Modifications of some of the foregoing conditions are occasionally considered as separate processes; thus, a large thrombus may exhibit a *central softening*, and postmortem or during an operation—*e. g.*, on aneurysm—a thrombus may be found in which liquefaction necrosis has occurred, converting the center of the thrombus into a reddish or yellowish fluid; this was at one time spoken of as cystic degeneration of a thrombus. An attached thrombus may remain more or less quiescent for a considerable length of time, or the changes that it may undergo may be so poorly marked as to be scarcely recognizable.

Results of Thrombosis.—These are largely dependent upon the character, location, and cause of the thrombus and upon the changes that the thrombus itself has undergone; the results due to such changes will suggest themselves: *e. g.*, an organizing or obstructing thrombus may more or less occlude the blood-vessel; the evidence of such occlusion will be dependent upon whether the blood-vessel is the main trunk to a limb or one of the less important branches; again, if the thrombus form slowly, the collateral circulation may sustain the nutrition to the limb or part. The alterations produced in the blood-vessel are dependent upon the changes that the thrombus undergoes; these also suggest themselves or have been indicated.

EMBOLISM.

An **embolus** is any body transported by the circulating blood, and capable, by reason of its physical characteristics, of obstructing the flow of blood in any part of the vascular system. As Park states, the essential element is transportation or carriage of some solid or semisolid body in the circulation. Oil and air, while not solid bodies, may be impacted within the capillaries, and hence may constitute emboli. The transportation and lodgment of emboli and in part, at least, the resulting changes constitute the process of **embolism.** Emboli are usually too large to pass the capillaries. They may be composed of: (1) Thrombi detached or in fragments. (2) Fragments of the cardiac valves or endocardial vegetations; the latter truly thrombi. (3) Calcareous plaques. (4) Fragments of morbid growths torn from tumor masses that have penetrated a vessel wall. (5) Purely extraneous bodies, such as bubbles of air, pieces of bone, or oil globules that may have gained ingress as a result of fracture or injury to bone; extensive laceration of adipose tissue may also give rise to oil embolism. The writer had an opportunity to observe a death from fat embolism following excision of the mamma for carcinoma; the patient was an unusually obese woman, fifty years of age. As a result of trauma, not only fat but fragments of tissue may enter the circulation; laceration of hepatic tissues may result in the displacement of fragments that, later, may be recognized in pulmonary infarcts. (6) Certain parasites, such as the echinococcus, filaria, etc., are transported by the circulating blood.

Thrombi or emboli are sometimes spoken of as (1) *arterial*, (2) *venous*, or (3) *capillary;* multiple; miliary; traumatic; neoplastic, arising from tumors; specific and nonspecific; simple and malignant: these terms explain themselves.

Occasionally, an embolus arising in the venous system passes directly from the right to the left side of the heart, through a defect in the septum between the auricles or ventricles, in which case it is spoken of as a **paradoxic** or **crossed embolus.** In very rare instances, as a result of sudden alterations in the blood-pressure affecting only one area, emboli may float backward in the venous stream, producing what is known as **recurrent embolism,** or they are called **retrograde emboli.** This was, at one time, assumed to explain certain abscesses of the liver, which are now known to be due to emboli arising in the portal system.

The most important classification of emboli is the division into

simple and **infective**, the terms having the same meaning as already given when considering thrombi.

Changes Induced by an Embolus.—An embolus floats along in the blood stream until it reaches the bifurcation of a blood-vessel either branch of which is too small to transmit the mass, or until it enters a vessel the progressive narrowing of which soon leads to its impaction; it obstructs or arrests the stream, and commonly leads to the formation of a thrombus; the blood supply transmitted by the occluded vessel is arrested, and the area beyond suffers from the altered circulatory conditions. The changes that take place in the affected area vary in degree, and are greatly influenced by a number of factors, among which may be mentioned the character and size of the embolus, the functional importance of the tissue involved, the presence or absence of an abundant collateral circulation, and the possibility of secondary infection or of a primary infection in a simple necrotic area. With regard to the character and size of the embolus, it may be said that, as a rule, massive emboli, such as dislodged thrombi of considerable size, are likely to obstruct the circulation of an area that may be sufficiently large at once to induce alarming symptoms or immediately fatal results. Thus, emboli of considerable size thrust into the pulmonary artery may lead to almost instantaneous death. For the production of this result it is not necessary that the circulatory arrest be dependent upon the occlusion of a large trunk; the scattering of a considerable number of small emboli (an *embolic shower*) brings about exactly the same result. The shape of an embolus may be such as only partly to obstruct a blood-vessel, and therefore not at once to cut off nutrition to the area beyond. Soft emboli plug vessels more completely than the more solid ones, which do not so readily mold themselves to the vessel lumen.

The functional importance of the tissue involved scarcely merits more than mere mention. Thus, it will be evident that a small embolus involving cutaneous, subcutaneous, or allied structures may induce so little change as to escape detection, while an embolus of the same size involving either the coronary artery or a cerebral area presiding over functions of great importance might, in either case, cause immediate death. The suddenness with which symptoms manifest themselves is also, to a certain extent, dependent upon the importance of the tissue involved. The possibility of at once establishing sufficient collateral circulation to supply nutrition to the area determines, to a large extent, the character of the subsequent changes. With the sudden stoppage of circulation the distal portion of the artery empties itself of blood,

and an area of ischemia is thereby induced. The sudden and persistent diminution in the intracapillary pressure favors the influx of blood from adjacent capillaries whose contained blood is, as a matter of course, directed in the line of least resistance. Coincident with the changes just mentioned dilatation of anastomosing or collateral arteries occurs, increasing the amount of blood traveling through those vessels. When the anastomosis between the artery involved and the arteries whose circulation still remains intact is sufficiently free, there is quickly formed a circulation adequate to maintain the nutrition in the previously ischemic area. With the establishment of sufficient collateral circulation the nutrition and function of the area may be resumed, while the changes that take place in the lodged embolus may be practically those already considered when discussing the changes to which a thrombus is liable.

In the absence of a sufficient circulation in the area, degenerative or necrotic processes occur. In the brain, in the spleen, and, to a certain extent, in the kidney, there is not, beyond a given point, a liberal anastomosis between the blood-vessels of adjacent areas. Such blood-vessels are said to be *terminal;* this implies that the tree-like branches given off by one vascular stem do not communicate with similar branches of adjacent vessels. The plugging of such vessels is followed by death (necrosis) of the area involved, which is now called an **infarct.** When the area remains ischemic (**anemic** or **white infarct**), the uncomplicated necrotic process presents the changes already described when considering coagulation necrosis. The area is wedge-shaped on section—truly cone-shaped, with the apex of the cone corresponding to the point of embolic obstruction and the base directed toward the surface of the organ. This typical cone shape is greatly modified by the presence of even a moderate degree of anastomosis at the periphery, and in large infarcts, or when multiple infarcts join, it may not be present. The consistence of the tissue is dependent upon the amount of coagulable material present. When the necrotic area has been infiltrated with lymph from the adjacent tissue, the swelling and increased density may be conspicuous. If the area be very large, the center may undergo fatty degeneration and may soften, converting it into a cyst; when liquefaction necrosis has followed the coagulative processes, the fluid may be absorbed and cicatrization may ensue. When the area is smaller, repair not uncommonly takes place. Proliferation of the connective-tissue elements occurs, resulting in the production of embryonic tissue and finally in cicatrization; into this lime salts may be infiltrated.

During the progress of the necrotic processes the resistance of the tissue to infection is greatly reduced, and not infrequently an infarct, resulting from a simple embolus, may develop suppuration. If the necrosis is so situated as to offer favorable opportunities for infection, the chances of its occurrence are greatly increased.

The foregoing description applies to the anemic infarct and to the process spoken of as *anemic infarction.* In some instances, after a varying period of anemia the capillaries of an ischemic area become overdistended with blood, admitted through adjacent communicating capillaries, or, possibly, by venous regurgitation; from the congested capillaries extravasation of blood into the connective tissue occurs, and, in addition to the coagulation necrosis in progress in the cellular elements of the area, a further fibrinous matting together results from the associated hemorrhagic infiltration. The resulting change constitutes a **hemorrhagic infarct,** and the process terminating in its formation is known as *hemorrhagic infarction.* The shape of the area is not altered by the occurrence of hemorrhagic infiltration. The swelling, however, is more marked; the color is dark red, at times almost black; and the density is greatly increased by the presence of the coagulated blood. The subsequent changes are the same as those occurring in areas of anemic infarction.

It has been held that an anemic or white infarct is but a later stage of the hemorrhagic form and that it is dependent upon the removal of the blood coloring-matter from the latter. It is possible that such a change occurs, and that the results of the two processes may be the same; but certain infarcts are apparently anemic from the beginning, and others are hemorrhagic early in their development.

The changes revealed by the histologic examination of the necrotic tissue will not be the same in different stages of the process. They are practically those already mentioned when considering coagulation necrosis. (See p. 250.)

In emboli containing bacteria (infective emboli), and in those containing the specific cellular elements of tumors (neoplastic emboli), arrest is followed by the development of the morbid process whose etiologic factor they transmit. If the embolus contains pyogenic organisms, an abscess is engendered; by reason of the constant presence of these abscesses in pyemia, they have long been known as **pyemic abscesses.** By reason of the fact that such abscesses change their location, they were called **metastatic abscesses.** Emboli containing tubercle bacilli induce tuberculosis at their point of lodgment. It is probable that the *amebic abscesses* seen in the liver arise as the result

of emboli brought from the intestinal lesion. A tumor infiltrating the wall of a blood-vessel, particularly a vein, may have swept into the circulation small fragments that projected into the blood stream, and these, in turn, arrested in the distant capillary, may resume their growth and give rise to a secondary tumor nodule, or *metastatic growth.* From the infected, parasitic, and neoplastic emboli secondary thrombi may form, from which, again, emboli may be broken off to continue the process of dissemination.

CHAPTER VI.

INFLAMMATION AND REPAIR.

INFLAMMATION.

Probably the most acceptable definition of inflammation is that given by Park, which is, as he states, a modification of Sutton's: "Inflammation is an expression of the effort made by a given organism to rid itself of or to render inert noxious irritants arising from within or introduced from without." It is probable that inflammation represents the process of repair plus infection or the removal of dead tissue, a relationship to be further brought out when considering the causes of inflammation.

Etiology.—As just indicated, inflammation is ordinarily produced by irritation or injury. The forms that these factors may assume are manifold, and any attempt to enumerate the various etiologic elements leading to inflammatory manifestations would lead far beyond the contemplated scope of the present article. The surgical tendency to consider inflammation as always the result of infection can scarcely be considered justifiable. After all, infection acts only by destroying the cells or irritating them by the noxious products of bacteria. It is true that bacteria are the most frequent irritants, and that a large percentage of the inflammatory processes arises as a result of bacterial activity. Bacteria or their products destroy or irritate the cells, and manifest a peculiar action upon the fixed and migratory cells of the economy, thereby inducing inflammatory processes more or less constant for each particular species of organism. The activity of the inflammatory processes induced by bacteria depends upon one or two factors: (1) the pathogenic power of the germ in question; (2) the degree of susceptibility of the tissues. As an example of the first condition it will be noted that if the two ears of a rabbit be inoculated with the anthrax bacillus or with the streptococcus pyogenes, using germs that are somewhat attenuated in one ear, and a more virulent organism for the other, there will be a decided difference in the local reaction as manifested in the two organs. Many experiments conducted along this line have led to conclusive proof that the pathogenicity determines to a large degree the activity of the ensuing inflam-

matory process. The importance of the second factor in the production of inflammation is equally well established. The susceptibility of the tissues may be augmented by reduced vitality; associated irritation, by the absence of immunity, either inherited or acquired, and by circulatory disturbances, or certain perversions of the nervous system. The susceptibility of the animal to a given infection undoubtedly varies at different times—a fact well shown by the occurrence of severe inflammatory processes after most trifling injuries, which, under other conditions, apparently give rise to little disturbance.

Injury to the tissue, whether it be mechanical, chemic, or thermal, is followed by the occurrence of the phenomena of inflammation; the extent of the inflammatory process may be dependent upon a number of associated factors. As just indicated, infection truly represents a chemic injury to the tissue, the noxious irritant being the specific product of the infecting organism. Inflammation may be induced by the injection of bacterial products without the presence of bacteria. Here we are dealing with chemic bodies alone. As further evidence of the phlogistic power possessed by chemic bodies may be cited the inflammation induced by the subcutaneous introduction of calomel, turpentine, croton oil, and similar irritants. That such inflammations are not purely of experimental production is established by their occurrence after the use of powerful antiseptics in too concentrated a form. There can be no doubt that the abundant use of mercurial solutions in wounds—a frequent procedure in early antiseptic surgery—led to necrosis of a large number of cells and to the occurrence of a certain degree of inflammation. Recognizing this, surgeons have adopted asepsis whenever possible. Even in infected areas abundant flushing with sterile fluids has been found to be attended with less local reaction than the use of even mild antiseptics. In a comparatively frequent form of conjunctival inflammation in the new-born, evidently the cause has not been the microorganism usually present (gonococcus), but the vigorous use of agents directed toward its destruction. In this instance and in the instances previously given the inflammation arises as the result of cell destruction brought about by agents directed toward the prevention of infection or toward the removal of existing organisms. The destruction of tissue and the production of exudates by chemic agents is further illustrated by the tissue reactions resulting from the application of so-called counterirritants, such as mustard, cantharides, turpentine, and chloroform, all of which induce an inflammatory response. Wounds of all kinds involve destruction of a varying

number of cells and injury to others. The wound made by the sharpest instrument is walled by a microscopic layer of lacerated cells. The more extensive the wound, the greater the number of cellular elements involved; and, of course, injuries made by dull, tearing, vulnerating bodies contain more lacerated cells than wounds of like extent made by sharp, clean-cutting instruments.

It will be observed that the whole list of inflammatory causes embraces at every turn the destruction of cells. The destroyed cells at once become irritants and induce inflammation in the adjacent viable tissues. The simple aseptic inflammatory reactions differ from the septic, in that the latter contain destructive agents that are constantly increasing, and, hence, the inflammatory processes seen in wounds made under aseptic conditions are but trifling as compared with the extensive inflammations following destruction of tissue associated with the introduction of infective agents that themselves further extend the cell necrosis and actively antagonize the process of repair. For this reason the surgeon has been led to regard repair as dissociated from inflammation, and to say that aseptic wounds heal without inflammatory phenomena. The pathologist must, however, recognize that all tissue injuries are attended by a certain amount of cell destruction, and that the effort made by the tissues to rid themselves of the dead elements constitutes, in a certain way, a part of the reparative effort. Still, with this admission before us we are to remember that the essential phenomena of inflammation and the essential phenomena of repair are, to a certain extent, dissimilar. Inflammation is attended by cell necrosis and degeneration; and repair by cell proliferation and regeneration. The possible admixture of the two processes can not be gainsaid. Of course, the same cellular elements at a given point are not evincing both processes, but one may be in close proximity to the other. The periphery of an inflammatory area nearly always shows, in the absence of rapid extension, a marginal zone of reparative effort. Were the effort at repair to remain quiescent until inflammation had terminated, repair would probably become an impossibility.

Morbid Anatomy.—The lesions to be studied in inflammation are: (1) The changes in the blood-vessels; (2) intravascular changes, or those occurring in the vessel contents; and (3) changes in the perivascular tissues.

Changes in the Blood-vessels.—These can be well studied in any vascular, transparent membrane, such as the tongue, mesentery, or web of the hind foot of a frog or the mesentery of any warm-blooded animal. If such transparent tissues be so ar-

ranged as to permit of their examination under the microscope, the following changes will be noted:

At the beginning of the examination the normal capillary presents itself as a transparent tubule, within which can be seen the circulating blood. As a rule, the application of an irritant is not necessary; exposure to the air, with the associated trauma incident to the arrangement of the tissue, will usually bring about the modifications to be observed. In other instances, as in the web of a frog's foot, it may be necessary to snip off with the scissors a thin layer of the epithelial covering, carefully avoiding any wound to the underlying blood-vessels. The blood-vessels at once contract, and at the same time the current is markedly accelerated; within the first hour after the injury the brief period of contraction is followed by beginning dilatation. At first the dilatation is regular; it then becomes varicose, and, in more marked cases, saccular projections of the capillary wall may be observed. Capillaries at first not recognizable, or at least not transmitting blood, dilate and become more or less distended. A similar dilatation of the arterioles, and particularly of the venules, is also to be noted. The changes so far observed are probably due to increased capillary tension and to the influence of the noxious agents directly upon the vessel wall. The rise in capillary tension is probably brought about by relaxation of the arterioles through which the blood supply to the part is admitted. The increased amount of blood present in the area is evident to the unaided eye. It is not possible at this stage to recognize any structural alterations in the cells that compose the capillary wall, nor are we able to see any enlargement of the capillary stomata, or any separation of the endothelial plates. A study of properly fixed preparations usually shows that the endothelial cells are swollen, and, when the process has lasted for any length of time, there is not uncommonly evidence of degeneration or proliferation, depending upon the activity of the noxious agent.

Changes in the Blood and Blood-current; Intravascular Changes.—Before the manifestation of inflammatory phenomena the stream within the capillary will be noted to be composed of two parts: (*a*) An *axial stream*, composed of the corpuscular elements of the blood, and therefore spoken of as the *corpuscular stream*; (*b*) a *circumferential* or *parietal stream*, composed of blood-plasma, and hence called the *plasmatic stream*. During the period of acceleration—a period that corresponds to the contraction and beginning dilatation of the capillaries—these two clearly differentiated divisions of the capillary contents are easily recognized.

With further dilatation and beginning slowing of the current the axial stream widens and the plasmatic stream grows correspondingly thinner. Within the first hour or so the narrowing of the plasmatic stream becomes marked, and instead of remaining clear, it contains a progressively increasing number of leukocytes.* At first these leukocytes roll along the vessel wall; later, they become attached at some point and hang off into the slowing stream as pear-shaped bodies, the small end of the pear corresponding to the point of attachment. The margination of the leukocytes is conspicuous in the small veins, but the size of even the larger dilated capillaries does not render the demonstration easy. As the dilatation of the blood-vessel becomes more marked there is poured out into the perivascular tissues a fluid derived from blood-plasma; this fluid constitutes the liquid exudate. Along with this certain of the leukocytes, as the result of their ameboid movement, pass through the vessel wall and reach the perivascular tissues. During the dilatation of the blood-vessel the blood-current becomes slower and slower, and shows only a slight progression with each heart-beat, and eventually oscillates in the capillary lumen; finally, this oscillation is arrested, and stasis or stagnation occurs. Before this final stage the differentiation into the axial and peripheral streams has disappeared, and the cellular contents of the vessel occupy the entire lumen. With the occurrence of stasis the red corpuscles at points arrange themselves in columns composed of cells piled upon one another (rouleaux). Migration of the leukocytes continues, and many of these cells present in the stagnant blood migrate toward the periphery and eventually reach the perivascular tissues. In properly fixed specimens the leukocytes can be seen in various stages of diapedesis. At first a pseudopod is projected through the capillary wall, appearing on the exterior as a small, roundish, knob-like protuberance. The extravascular portion of the cell increases in size by the protoplasm of the cell flowing through the narrowed portion into the extravascular projection. Finally, the nucleus passes through, and apparently the solution in the continuity of the vessel wall disappears. (See Fig. 187.) After the migration of the leukocytes and the lessening of the intracapillary tension by the pouring-out of the exudate, resumption of circulation may be at times observed.

To a certain extent the character of the irritant determines the

* Before attempting to follow the various steps of diapedesis and the functions of the leukocytes in inflammatory and reparative processes, the student is advised to familiarize himself with the table describing and differentiating the leukocytes. (See chap. I, of part III.)

form of leukocyte most abundant in the exudate. In many of the infections, and particularly in pyogenic infection, the finely granular oxyphile cell (polymorphonuclear leukocyte or microphagocyte) is abundant. In other inflammatory conditions the hyaline cell (macrophagocyte) is most abundant. Exactly what factors determine the occurrence of one or the other of these cells has not been definitely ascertained. It would seem, however, that in the more acute, and particularly in the suppurative, inflammatory conditions, as already stated, the microphagocyte is abundantly present; in the more chronic lesions, with less active irritants, the macrophagocyte is in excess. It is not possible to affirm, however, with any degree of definiteness, in the present stage of our knowledge, exactly what conditions determine the presence of one or the other of these phagocytes.

As to the causes leading to the occurrence of migration and

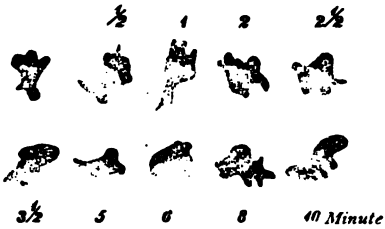

FIG. 187.—LEUKOCYTES OF A FROG.—(*Stöhr.*) × 560 diameters.

Extending out from the side of the leukocyte will be seen a number of projections, called pseudopods. In the diapedesis or migration of the leukocyte through a blood-vessel wall in inflammation these pseudopods are first thrust through the wall, the cytoplasm of the leukocyte flowing through into the pseudopod, carrying with it the nucleus, thereby delivering the cell upon the outer side of a blood-vessel wall.

to the development of the exudate, two views have been held. It was long maintained that it was purely a physical process; the increased vascular tension, with the associated alterations in the capillary wall, led to the escape of part of the fluid contents of the vessel. By this theory the vessel wall was presumed to be passive. Later investigations have seemed to establish an entirely different opinion. Under the older view it was believed that the fluid normally present in the lymph-spaces of the various tissues was filtered through the vessel wall as a result of the intravascular tension. Later observers hold that the endothelium of the capillary secretes this fluid, and that instead of being a transudate, as originally thought, it is purely a secretory product of the endothelium. Admitting the correctness of this view, the material that we have been considering as an exudate must now be considered, at least in part, a secretion. The technical

difficulties that surround efforts to demonstrate the correctness of either theory have been so great that neither is at present deemed fully acceptable. The theory that the migration of the leukocytes is dependent upon increased vascular tension can not, of course, be maintained, as wandering cells already present in the tissues adjacent to an inflammatory area show migration toward the center in spite of the fact that such migration must be in the direction of the point of greatest pressure.

Changes in the Perivascular Tissue.—In the perivascular tissues two distinct classes of elements must be considered: (1) Changes occurring in the elements normally present; (2) changes that follow in the fluids and cells coming from within

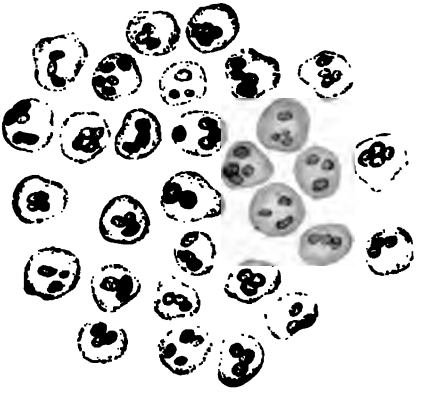

FIG. 188.

Pus-cells under high magnification from center of one of the infiltrated areas in a section of the cerebral cortex and meninges from a case of suppurative meningitis. Section stained with toluidin-blue.* (Zeiss $\frac{1}{18}$-inch oil immersion; Queen oc. B.)

the vessels. It has been stated, and apparently correctly, that changes occurring in the normal perivascular structures are essentially the same as those seen in tissues that are normally nonvascular. As a type of such tissue, the cornea may be studied. The corneal tissue is abundantly supplied with lymph-channels, but contains absolutely no blood-vessels. The lymph circulating through the corneal lymph-spaces is derived from the capillary circulation surrounding the organ. Destruction of a small, superficially placed central area of the cornea by means of chemic irritants, or the removal of a thin

* The microscopic drawing made from this section will be found in the chapter on Diseases of the Nervous System, under the head of Suppurative Meningitis.

superficial layer is followed by opacity at the point of injury, extending as a zone of haziness for some distance beyond. The preliminary degenerative changes in the corneal corpuscles are quickly followed by reparative efforts. Leukocytes surround and eventually infiltrate the area, while the undestroyed connective-tissue cells (corneal corpuscles) begin to show evidence of proliferation. The proliferative changes manifested in the corneal corpuscles are evidently the initial steps in the process of repair. The leukocytes present in the area could not have arisen as a result of increased pressure directed toward the point of injury, but must be present as the result of some other factor. This leads us to discuss causes inducing the evident migration of leukocytes toward the area of injury.

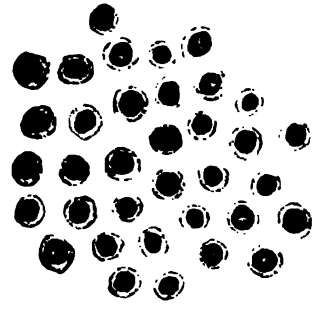

FIG. 189.
Lymphoid cells from meninges in a case of tuberculous meningitis. Section stained with toluidin-blue. (Zeiss $\frac{1}{12}$-inch oil immersion; Queen oc. B.)

De Bary observed that certain plasmodia moved toward the nutritive material placed in their vicinity, and a further study showed that at least three classes of substances could be recognized: (1) Substances toward which the plasmodia moved; (2) substances that did not seem to influence the organism; (3) substances from which the organism receded. This property of cellular attraction and repulsion is called **chemotaxis,** or **chemiotaxis.** When the cell is evidently drawn toward the body, the condition is called *positive chemotaxis;* when repelled, *negative chemotaxis.* Positive chemotaxis is admitted. Negative chemotaxis interests us but little; the existence of such a condition has been doubted, although experimental evidence would indicate its occasional occurrence. Experiments are not wanting to show that leukocytes travel toward certain infecting bodies, and that dead tissue is apparently attacked by these cells. The ultimate explanation of chemotaxis is still wanting; we do not know whether it is a chemic affinity or a phenomenon allied to diffusion in simpler bodies, or whether it is an essential characteristic of certain cells not dependent on known chemic and physical explanations applicable under what seem to be similar circumstances.

The cells influenced by positive chemotaxis arrive at the area of irritation from two directions: from the blood-vessels

come the polymorphonuclear leukocytes in large numbers, while from the adjacent connective-tissue spaces come the large hyaline cells and eosinophiles. Eventually, the field of observation becomes so clouded by the cellular elements present that continued study of the previously transparent tissue is no longer possible. Whether all the leukocytes present in the area came from the sources just indicated or whether some of them are the result of proliferation has not been definitely determined. It is reasonable to conclude, from data at hand, that a certain number of the leukocytes result from proliferation of migrated cells. That this number is large, or that proliferation constitutes an important process in the production of the large number of cells present, seems doubtful.

The changes that take place in the fixed cells of the tissue involved, as well as the alterations that the invading cells may undergo, are dependent upon a number of conditions. If the irritant be active,—as, for example, the poison of virulent bacteria,—many of the cells are at once destroyed. When the pathogenicity of the irritant is less marked, degenerative changes may be more conspicuous than actual cell death. The characteristics of these degenerative changes will vary in different tissues, and are more marked in organs whose cellular constituents are largely of epithelial origin. In the liver and kidney the degenerative phenomena that attend inflammation may be more conspicuous than the exudate. In such epithelial structures cloudy swelling, fatty degeneration, and hydropic distention of the cells with nuclear fragmentation may be conspicuous. In the connective tissues mucoid and hyaline transformation may be present. The amount of degenerative change and the associated cellular disintegration are also dependent upon the intensity of the irritant; such degenerations are most marked in the various infections of which the pyogenic constitutes a typical example.

The fluid exudate now present in the perivascular tissues varies in quantity and composition. The quantity is dependent upon the character of the irritant as well as upon the tissue involved. The more richly vascular the area, as a rule, the greater the amount of the exudate. Loose connective tissues, such as the eyelid, scrotum, and labia, show marked accumulation of exudative fluids. The same is commonly true of serous membranes, and, to a lesser degree, of the subcutaneous and submucous connective tissues. The fluid differs in chemic composition from the fluid in edema; its specific gravity is higher (edema, about 1.010, rarely over 1.015; inflammatory exudate, 1.020 to 1.025); it is highly albuminous, not uncommonly containing

five times the quantity of proteids present in edema fluids; it is rich in fibrin. When bacteria are present, the fluid usually contains peptone, which, in old suppurative processes or when the lesion is extensive, may enter the general circulation and may be excreted in sufficient quantity to be recognizable in the urine. For evident reasons the inflammatory exudate is rich in cells, an abundance of which may render the fluid quite opaque.

The leukocytes brought into the area by any of the processes indicated at once attack the infecting organism,—if bacteria be the cause of the inflammation,—or proceed to remove the dead tissue when the inflammatory process is associated with, or has arisen secondary to, cellular destruction. The phagocytes active in this process have been mentioned. As already stated, when considering phagocytosis in its connection with immunity, it is not improbable that certain phagocytes liberate antitoxic or bactericidal bodies that exert a certain amount of influence in subduing infection. (See Phagolysis, p. 156.)

The fluid portion of the exudate relieves the intravascular tension by its escape, dilutes the irritant present in the tissues, carries with it antitoxic and bactericidal properties, and possibly in some instances affords increased nutrition (?) to the cells of the area. The fibrin-forming bodies contained within the exudate reaching the perivascular tissues form fibrin, which acts not uncommonly as a limiting body, retarding the dissemination of bacteria and lessening the rapidity with which the toxic bodies present are diffused into the surrounding tissues. Its function in the repair of wounds will be considered later.

Terminations of the Inflammatory Process.—These are largely dependent upon the activity and persistence of the cause, as well as upon the susceptibility of the tissue, including under this term the activity of the protective agencies whose tendency is always directed toward the arrest of irritant action. When the etiologic factor is readily overcome, or is quickly withdrawn, restitution to the normal may be brought about without leaving any evidence of a past inflammation. In the early stages of the inflammatory process the withdrawal of the cause will be quickly followed by absorption of the exudate and the reestablishment of the circulation. The exudate passes off by the lymphatics or is taken up by the veins, and the few extruded leukocytes reenter the circulation, either directly, through the blood-vessels, or indirectly, through the lymphatics, eventually leaving no recognizable tissue alteration. As the inflammatory process continues, so favorable a termination becomes less and less possible, until finally the tissue alterations are such that a return to the normal

is no longer to be expected. Under such circumstances the occurrence of repair is the best that can be expected; and the longer such repair is delayed, the less effectual it is likely to be. The most important factor in the prevention of repair is infection; and the more active this infection, the more grave the tissue alterations will be, and the less perfect the subsequent repair.

Suppuration.—The organisms most active in the production of suppuration are the staphylococci and streptococci—pyogenic cocci. While the foregoing are the usual bacteria active in suppurative processes, it is not to be forgotten that many other organisms share this pus-producing power. Thus, the bacillus coli communis, bacillus pyogenes fœtidus, bacillus typhosus, gonococcus, micrococcus cereus flavus, micrococcus cereus albus, pneumococcus, the fungus of actinomycosis, bacillus pyocyaneus, bacillus anthracis, and other organisms, occasionally manifest pyogenic activity. In most instances suppuration is due to a mixed infection. Commonly, at least two organisms are present, and in many instances a number may be associated. A series of unpublished investigations conducted by Lockett in the writer's laboratory showed that of one hundred consecutive suppurative processes, a single infection was the exception. These observations are corroborative of many similar studies made by other observers.

Abscess.—In infection by pyogenic organisms the continued action of the irritant (a necessary sequence of bacterial proliferation and of the continued production of toxins) prolongs the period of exudation and necrosis and increases the quantity of the exudate, which is particularly rich in phagocytic cells, the most abundant of which is the finely granular oxyphile cell. The bacterial products lead to degenerative changes in the fixed tissue elements, associated with liquefaction of the intercellular substance, converting the area so affected into a mass of cellular detritus in which the cell longest retaining its morphologic characteristics—the finely granular oxyphile cell, now the pus-corpuscle—is most abundant. The fluid resulting from these changes is called pus. Pus is a creamy fluid possessing a faint, sweetish odor; its specific gravity ranges between 1.020 and 1.035, with a mean of about 1.032. Essentially, pus is composed of two elements—the fluid and cellular portions. The fluid constituent is called the *liquor puris;* it represents the fluid portion of the exudate, to which has been added the fluid resulting from the liquefaction of the intercellular substance and, possibly, from the dissolution of a number of the tissue elements, and, it may be, of some of the cells. It is comparatively rich in

albumoses, to which the absence of coagulability has been attributed. It also contains leucin and tyrosin. The pus-cell is richly granular, usually polynuclear or polymorphonuclear, and for a brief period following its removal from the body may show well-marked ameboid movements; in its present form it can not be differentiated from the polymorphonuclear or finely granular oxyphile cell, which earlier reached the inflammatory field from the blood-vessel. With regard to the hyaline or mononuclear cell, occasionally present in pus, our information is less satisfactory; the tendency at present is to regard these cells as invaders from the adjacent connective-tissue spaces—in other words, they are believed to be celomic wandering cells. In the production of the abscess liquefaction first takes place at the center of irritant action, from which, as we pass outward, toward the surrounding uninvolved tissue, all intermediate stages of the inflammatory process may be recognized. The *wall of the abscess* is, therefore, composed of the normal tissues of the part, showing various degrees of inflammatory infiltration, degeneration, and necrosis. The zone lying nearest to the pus is composed of necrotic tissue rich in leukocytes. Surrounding this will usually be seen a zone containing the exudative fluids and numerous white blood-cells. There is usually present more or less fibrin entangled among the fixed connective-tissue cells, the latter not uncommonly showing proliferative changes. In this zone efforts at repair and at the prevention of dissemination may be evident. Externally, this zone gradually fades into the normal tissue, and internally it is continuous with the necrotic zone to which reference has already been made. If let alone, the abscess tends to travel along the path of least resistance; as the infective agents tend to extend in all directions, but are met by the protective forces of the tissues, the path of least resistance must be through those tissues where the protective agencies are least active. The vascularity of the part, and hence the richness in leukocytes, usually results in the extension of the abscess toward the surface, through which it eventually ruptures and discharges its contents. Relieved of this tension, the direction of the fluid exudate is now strongly toward the abscess cavity. This results in the flushing out of the surrounding lymph-spaces, and favors the action of the protective forces —the phagocytes, antitoxic and bactericidal bodies present in the inflammatory area. When the infective organisms are destroyed or rendered inert, the liquefaction and formation of pus cease; after incision and evacuation the walls of the abscess collapse, and reparative efforts become ascendant.

Ulceration.—The younger Gross often spoke of an abscess as a subcutaneous ulcer, and in the present state of our knowledge many ulcers could, with propriety, be called superficial or, more correctly, exposed abscesses. Where suppurative processes are so situated that a wall is formed on but one side,—in other words, are exposed,—the floor of the ulcer is structurally quite like the wall of an abscess. This applies, of course, only to ulcers in which infection is active. Exposed or denuded subcutaneous tissues where the removal of the overlying structures has been brought about under strict aseptic precautions bear little resemblance to the formative stage of an abscess. When, however, the ulcer has resulted from infective processes, giving rise to necrosis of the overlying structures, the early stages of ulcer formation are practically identical with those seen in the wall of a developing abscess. The pus formed by such ulcers finds ready egress, and the protective powers of the underlying tissues usually limit and arrest the spread of the ulcerative lesion. Occasionally, however, ulcers show continued necrosis, gradually extending in one or more directions, thereby indicating the inefficiency of the protective powers in the adjacent tissues. The fact that such ulcers appear to extend in one or more directions, as though something were eating away the tissues, led to their being called *phagedenic.*

In addition to abscess formation and ulceration, there are allied forms of infection in which the anatomic peculiarities of the tissues involved, or the absence of resistance, or the intensely toxic power of the infection, give rise to changes resembling abscess formation, but by no means identical. Closely allied to abscess formation is the occurrence of suppurative lesions of the serous membranes. Here the collection of pus takes place in the serous cavity, and is not usually referred to as an abscess. (For the description of suppurative inflammation of serous membranes, see Disease of Serous Membranes, part III.) Suppurative processes leading to the accumulation of pus in cavities lined by epithelium occur. As in serous cavities, these are not usually referred to as abscesses; thus, purulent accumulations in the pelvis of the kidney are spoken of as "pyonephroses," and in the Fallopian tube purulent distention is called "pyosalpinx."

At times the extension of infection proceeds with such rapidity that a distinct accumulation of pus may not be evident. Thus, in inflammation of the cellular tissues, and in inflammation of the lymph-vessels (angioleucitis) due to virulent infection or to greatly reduced resistance on the part of the individual, the

inflammatory process may extend with remarkable rapidity, and may even terminate fatally before the occurrence of any recognizable purulent collection. Sometimes along the paths of such rapidly spreading infections a variable quantity of macroscopically recognizable pus may be developed. Such a condition is sometimes referred to as *diffuse suppuration*, *suppuration of the cellular tissues*, *purulent infiltration*, and, without any apparent reason, is sometimes called *purulent suffusion*.

The occurrence of gangrene as a result of infection has already been considered. (See Spreading Gangrene.)

The terms *acute*, *subacute*, and *chronic*, as applied to inflammatory processes, are used to indicate, to a certain extent, the period of time, or duration, as well as the activity of the inflammation, and, under certain circumstances, its location and sequels. That form of chronic inflammation in which the process extends over a long period of time and is associated with the formation of fibrous tissue in excess is sometimes referred to as *productive inflammation*. The changes that take place in the interstitial tissue of the kidney in chronic interstitial nephritis may be taken as a type of this form of inflammation. (See Chronic Interstitial Nephritis, chapter on Diseases of the Urinary Organs, part III.) The view that all tissue changes associated with an increase in fibrous tissue are to be regarded essentially as manifestations of productive inflammation is no longer strongly urged. Thus, in degenerations that involve parts of the glandular viscera the disappearance of the essential normal elements may be followed by the development of fibrous tissue. This is sometimes spoken of as "substitutive fibrosis," and by some is not considered to be an evidence of past or existing inflammation. Such increase in fibrous tissue is spoken of as "noninflammatory hyperplasia," thereby differentiating it from the increase in fibrous tissue that is clearly consecutive to inflammation and constitutes the terminal tissue changes in many inflammatory processes. When considering the pathology of organs, further reference will be made to chronic inflammatory processes and substitutive fibroses. (See Interstitial Pneumonia and Cirrhosis of the Liver, part III.)

Inflammatory processes not associated with infection are sometimes spoken of as simple or common. To speak of such processes as common in the sense that they are frequent is probably an error, as most inflammations are due to infection. Inflammations due to some particular organism, or even when the organism is not known, as in chancroid, are called specific. While not restricted to syphilis, the term specific infec-

tion is most frequently applied to syphilitic lesions. When the essentially secreting or actually functionating cells of the organ are involved, the inflammation is spoken of as *parenchymatous;* when the interstitial tissue (connective tissue) is the principal seat of the lesion, the inflammation is called *interstitial.* By reason of the intimate physiologic and structural relation of the connective tissues of organs with the essential functionating cells it does not seem probable that an inflammation could ever be strictly parenchymatous or strictly interstitial. That one or the other tissue may be apparently more involved justifies, to a certain extent, this nomenclature. Suppurative, pyogenic, purulent, or phlegmonous inflammations have already been considered. Such inflammations are appropriately called septic, in contradistinction to the inflammatory conditions in which bacteria have no part—*aseptic inflammations.* When considering inflammations of the mucous membranes, reference will be made to catarrhal, pseudomembranous, fibrinous, croupous, diphtheric, gangrenous, suppurative, and hemorrhagic inflammations of those structures. (See Diseases of the Mucous Membranes, part III.) Dry, moist, serous, serofibrinous, fibrinous, plastic, adhesive, exudative, and other inflammatory processes affecting serous membranes will be considered with diseases of those structures. (See Diseases of Serous Membranes, part III.)

It will not be amiss, at this point, briefly to discuss the cardinal symptoms of inflammation and to indicate the relation that exists between these usually recognizable changes and the morbid processes to which they owe their presence. The more or less active inflammatory conditions, and even certain inflammations characterized by sluggishness, possess one or more of the so-called cardinal symptoms: namely, heat, pain, discoloration, swelling, and disordered function.

Morbid Physiology of Inflammation.—*1. Heat.*—Practically, the recognizable rise of temperature is dependent upon the increased amount of blood distributed in the area, which, coming from internal organs, possesses a temperature higher than the blood present in the superficial circulation under normal conditions. Theoretically, the following features are also active; it is not probable, however, that their influence is of practical import: (*a*) the increased cellular metamorphosis; (*b*) the increased oxidation that is going on in the area involved; (*c*) the friction of the increased blood-currents and the impact of stasis may also increase the temperature.

2. Pain is due to pressure or to stretching of the nerves by the swelling, and to the irritant action of the inflammatory exudates

upon the nerve filaments. At this point it is well to note that pain may be beneficent in inflammation, in that it secures rest of the part, thereby leading the patient to favor the progress of reparative processes.

3. Discoloration is dependent upon (*a*) the increased amount of blood in the area; (*b*) the proliferation of the cellular elements; and (*c*) the character of the inflammatory exudate; thus, the increased amount of blood may give rise to redness, which becomes scarlet, brownish, or bluish, passing through the different shades to black. In nonvascular exudates the structure may be white instead of red; this is shown in the cornea, where occurs the ground-glass appearance, due to the inflammatory products, there being no red blood-corpuscles in the cornea. Redness, when present, is represented by the injection of the adjacent conjunctiva. The exudate in inflammations of serous membranes renders the surface white, unless the inflammatory processes be hemorrhagic.

4. Swelling is due to (*a*) the increased amount of blood in the part; (*b*) the proliferation of the cells; (*c*) the exudate in the perivascular tissue. As already stated when considering the development of the exudate, swelling may manifest beneficial tendencies. (See p. 289.) Under certain circumstances it becomes dangerous; thus, if the swelling be great, the capillary circulation may be obstructed, and, as a result of faulty nutrition and of the activity of the inflammatory process, degenerative changes, necrosis, and even gangrene may occur. This unfortunate termination is sometimes observed in inflammation of the subcutaneous tissues (cellulitis, angioleucitis), where the extensive swelling cuts off nutrition to the overlying structures and gangrene ensues. Inflammation of the juxta-epiphyseal disc may lead to thrombosis of the capillaries supplying the epiphysis, followed by necrosis of that structure. It is not necessary to multiply examples, although reference should be made to the corneal sloughing that takes place as a result of intense swelling of the surrounding conjunctiva, cutting off ingress and egress of lymph from the avascular, transparent membrane.

5. Disordered function is due to (*a*) alteration in the tissue cells present, both the essential functionating cells and the interstitial elements; (*b*) the mechanical interference with function resulting from the exudates; and (*c*) the fact that the exudates prevent the activity of the innervation upon which the function of all tissue so largely depends.

Systemic Phenomena of Inflammation.—These are largely embraced in the term *fever*, and are due to the absorption of the

inflammatory materials from the seat of the morbid process. The character of the fever and the severity of its manifestation are dependent upon the activity of the agents absorbed. In the simple aseptic fluids taken up by the lymphatics from an ordinary sterile wound, such as is typified in a broken bone, the manifestations are slight and temporary. When the materials absorbed contain the products of bacterial life, marked alteration in the tissue elements elsewhere in the body may occur. Degenerative processes arise in the viscera independent of the presence of bacteria. The disturbances of glandular activity are represented in the diminished secretions and excretions. The epithelial surfaces show, under the influence of bacterial agents, a decided tendency to undergo degenerative processes; this is most marked the more severe the infection, so that in the gangrenous and specific inflammations—for example, those of diphtheria—coagulation necroses in the large glandular viscera are not uncommon. The nervous phenomena that accompany inflammation are probably due to the direct action on the nerve substance of the poison under consideration, or to the influence of the poison upon the capillaries distributed in the nerve tissues, giving rise to inflammatory or degenerative processes in those structures. Exactly what causes the condition called fever will be discussed later.

REPAIR.

Cell Reproduction.—As a part of the processes of repair (repair modified by infection, regeneration, inflammation so called, hyperplasia, certain forms of hypertrophy, etc.), proliferation, proliferation, or reproduction of cells must be studied. There are two methods by which cells are reproduced: (1) *Direct division*, or *amitosis;* (2) *indirect division*, also known as *karyokinesis*, *karyomitosis*, and, quite commonly, a more convenient term, as *mitosis*.

1. **Amitotic Division.**—In this form of segmentation the cell shows a constriction that involves both the cell protoplasm and the nucleus. This constriction is followed by a separation of the two portions, the nucleus first dividing and passing to the two ends of the protoplasm, which gradually separates, giving rise to two cells; during the process there is no manifest systematic change in the chromatin of the nucleus, as is seen in the next form.

2. **Mitosis.**—As a rule, the cell divides only into two parts; this is not, however, constant, as occasionally three cells may be developed simultaneously from one cell (J. Arnold). The steps

of mitosis may be approximately stated as follows: In the resting nucleus the chromatin increases and groups itself as a skein, which later becomes thinner (*mother skein*). During this process the nuclear membrane disappears, and, if the cell possessed a nucleolus, this is lost sight of. Immediately following this—probably in progress at the same time—there are soon developed, apparently from the achromatin, delicate lines that pass off toward the two poles of the cell, giving the central portion of the cell an arrangement shaped like a spindle, and hence the name *nuclear spindle*. The chromatin now divides transversely to this

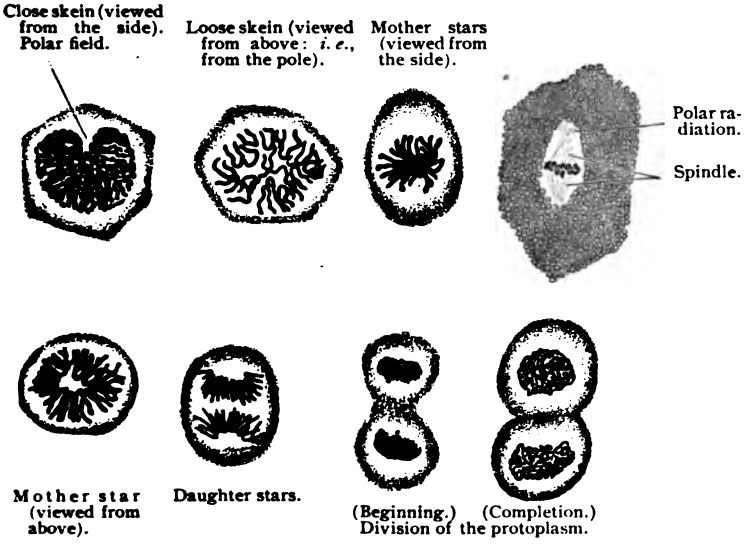
Close skein (viewed from the side). Polar field.
Loose skein (viewed from above: i. e., from the pole).
Mother stars (viewed from the side).
Polar radiation.
Spindle.
Mother star (viewed from above).
Daughter stars.
(Beginning.)
(Completion.)
Division of the protoplasm.

FIG. 190.—KARYOKINETIC FIGURES OBSERVED IN THE EPITHELIUM OF THE MOUTH CAVITY OF A SALAMANDER.—(*Stöhr.*) × 560 diameters.

The picture in the upper right-hand corner is from a section through a dividing egg of siredon pisciformis. The centrosomata, also the first stages of the development of the spindle, can not be seen by this magnification.

nuclear spindle, and passes, one half in each direction, toward the points of the spindle. The mass of the chromatin at each end of what was the spindle now constitutes what are spoken of as the *daughter stars*. During the arrangement of the chromatin as daughter stars an hour-glass-like contraction of the protoplasm of the cell appears, formed by an annular narrowing gradually developed around the center of the cell. At first the daughter stars situated in the two poles of the cell are joined by delicate striation, which probably represents the remains of the achromatin formerly constituting the nuclear spindle; these lines disappear,

the two masses of chromatin show now no connection, and the hour-glass contraction is completed, separating the cell into two parts, in each of which parts there is a daughter skein, which now rearranges itself as a resting nucleus, around which a new nuclear membrane may appear.

Lavdowsky has described another form of cell division that he calls *division by force*. It appears in this form: two portions of the protoplasm of the cell move in opposite directions, apparently pulling themselves apart. Thoma has described and illustrated this process as occurring in the white blood-cells of the frog when stimulated by electricity.

Inflammation is repair plus the removal of dead tissue or infection. When there is no dead tissue to remove, or when this is in a minimum, and when there is no infection, injury to tissue is followed immediately by the process of repair.

As studied by the surgeon, healing is said to take place in the following ways:

1. **Union by First Intention.**—Thus, if the surfaces of a recent wound be brought immediately in contact and retained, the following phenomena occur: Liquor sanguinis is poured out, immediately followed by its coagulation, forming a fibrinous cement —the so-called inflammatory lymph—that binds the two sides of the wound together. Into this leukocytes wander from the adjacent blood-vessels, and, by means of their phagocytic action, they proceed to the removal of the dead tissue. Proliferation of the fixed connective-tissue cells rapidly ensues, leading to the formation of *embryonic tissue*. It is now generally conceded that embryonic tissue is largely the product of the fixed connective-tissue cells. It can not, however, be established, beyond the possibility of doubt, that the migrated leukocytes have nothing to do with its formation. Particularly is this true when we consider that many of the cellular elements present can not be distinguished, either morphologically or tinctorially, from the hyaline leukocyte. Many of the cellular elements present in such tissue show active mitosis, and eventually lead to the formation of fibrous, cicatricial, or scar tissue. By reason of what appears to be the specific function of such cells they are called *fibroblasts*. Exactly how fibrous tissue is formed by or from the fibroblasts is not fully determined. It is held by some that the fibrous tissue is laid down by the fibroblasts, partly as a secretion, in a manner similar to the laying down of cartilage and bone by chondroblasts and osteoblasts respectively. By others it is held that a part of the fibroblast becomes actually transformed into the new fibrillated elements. Among the other cellular ele-

ments of doubtful origin and often observed in reparative processes are giant-cells. The origin, structure, and function of giant-cells have been the source of much controversy since their description by Johannes Müller in 1838. They probably arise in one of two ways: (1) Nuclear division without associated protoplasmic segmentation; (2) confluence of the protoplasm of cells, resulting in the formation of a type of giant-cell resembling that caused by the massing of other cells, called plasmodia. The number of nuclei present in the giant-cell varies; as many as eighty have been observed in a single cell. The researches of Heidenhain, Koch, Metschnikoff, Soudakewitsch, Faber, and

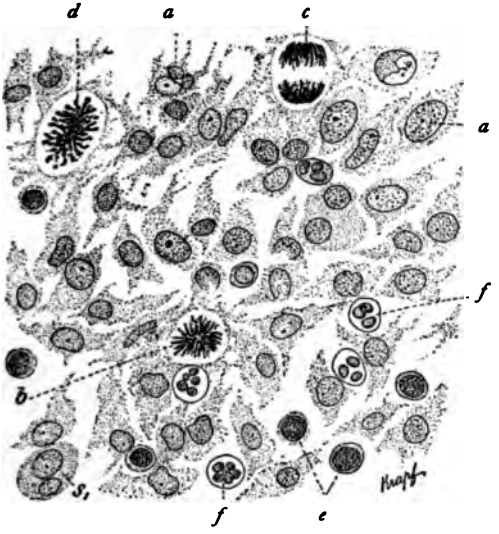

FIG. 191.—CELLULAR ELEMENTS OF GRANULATION TISSUE.—(*Schmaus.*) × 500 diameters. *a, a.* Spindle-forming, star-forming, and round cells. *b.* Mother star. *c.* Daughter star. *d.* Skein stage. *e.* Round or lymphoid cells. *f, f.* Polymorphonuclear leukocytes.

others seem to establish the inclusion and phagocytic power of giant-cells.

In order to maintain the nutrition of the developing tissue blood-vessels are necessary. While in the embryo other forms of capillary development are recognized, the only form admittedly present in reparative processes is development by budding. From the walls of the nearest capillaries there extend conic projections into the developing tissue. These projecting buds, after passing some distance from their point of origin, unite with other buds, thus forming loops, through which the circulation is established.

The tissue previously known as embryonic tissue is now *granulation tissue*. When seen, for example, in the floor of an ulcer, each loop or group of loops forms a minute elevation called a granule; hence the name granulation tissue. It is possible that capillaries formed in this way may later develop thicker walls, and may ultimately become arteries or veins. Around the newly formed capillaries the development of fibrous tissue continues. At first the cicatrix-scar is red, or at least pinkish, the heightened color being due to the richness of its blood supply.

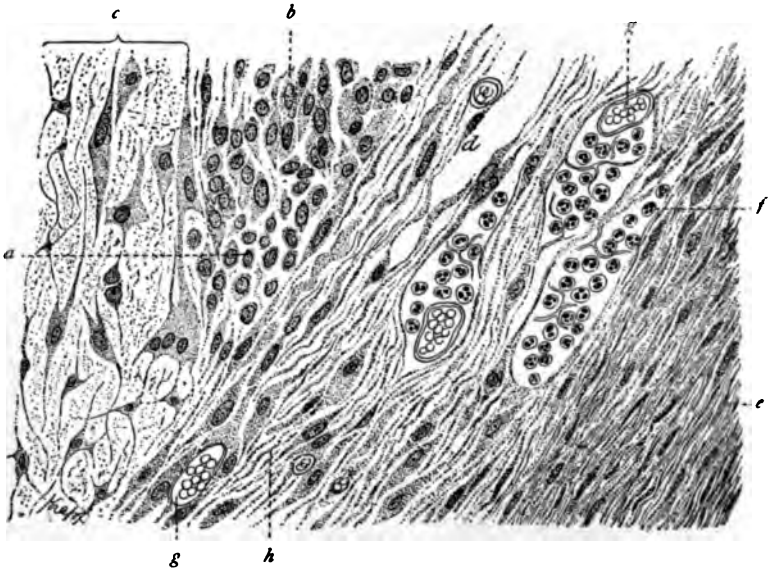

FIG. 192.—GRANULATION TISSUE. LATER STAGE IN ORGANIZATION THAN FIGURE 191.—(*Schmaus.*) × 250 diameters.

a. Round or lymphoid cells. *b*. Fibroblasts. *c*. Spider cells, multipolar cells. *d*. Space from which cellular elements have dropped out; possible primitive lymph-spaces. *e*. Point where the evolution of fibrous connective tissue is most advanced. *f*. Leukocytes with several nuclei. Through this area will be seen young capillaries, branched and budding; the same are shown below the blood-vessel indicated by the upper *g*. *g*, *g*. Blood-vessels. *h*. Matrix of intercellular substance forming fibrillated tissue.

Later, contraction of the interlacing fibrous tissue occurs, diminishing, by pressure, the number and carrying capacity of the newly formed vessels, the tissue eventually becoming white. The tendency of developing fibrous tissue to contract gives rise to structural and functional disturbances in organs whose nutrition it so profoundly influences. The evidence of such contraction is clear in diseases of certain viscera, such as the liver in chronic interstitial hepatitis, and the kidney in chronic interstitial nephritis.

There is sometimes described a form of repair that closely resembles union by first intention—repair upon a *framework* or *scaffold.* To illustrate how this may occur, let us suppose that there is a large "dead space," such as would result from chiseling a cavity in bone; into this dead space blood oozes and coagulates. The coagulated fibrin forms a scaffold, upon which young blood-vessels and embryonic and granulation tissue advance from the sides and eventually complete the process of repair. Materials other than blood have been used for the scaffold; sponge, chips of bone, cartilage, ivory fragments, and allied substances that can be readily antisepticized may be used.

2. Healing by second intention is said to occur in wounds the edges of which can not be brought together, and in which the scaffolding process, already referred to, is not available. The

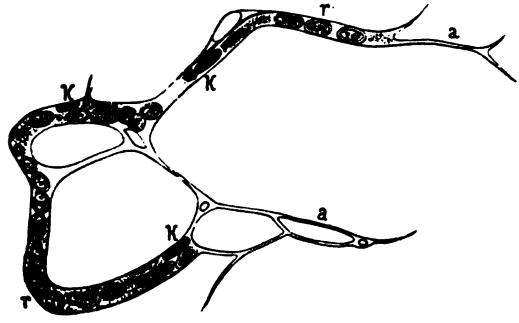

FIG. 193.

The formation of capillaries in embryonic tissue. *K, K, K.* Endothelial plates with protoplasmic projections, *a, a,* which later become capillaries. Other communicating branches are shown. A part of the vascular loop contains red blood-cells, *r, r.*—(*Landois.*)

ordinary recent traumatic ulcer is an illustration of this process. Suppose that considerable skin surface is removed, and that a raw surface is presented for healing: Within a few hours a layer of coagulated fibrin and partly inspissated serum will be seen upon its surface. Dead elements are attacked by the phagocytes and are removed, and proliferation of the connective-tissue cells and leukocytes proceeds to the formation of embryonic tissue. Young capillaries spring out from the adjacent vessels and convert the embryonic tissue into granulation tissue. By continuous proliferation of the cellular elements, with pushing up of the capillaries, the cavity is gradually filled, and when this new tissue reaches the surface, covering over by epithelium occurs.

The epithelial regeneration is secured through the activity of the epithelial cells near the edge; these proliferate, and by ex-

tension from the periphery, in favorable cases, gradually cover the granulating surface. Epithelium may be ingrafted upon the embryonic tissue, and new centers of epithelial regeneration may be thus established.

Another form of healing that is truly repair by second intention is sometimes referred to as **healing by third intention.** This is illustrated when two granulating surfaces are brought together; the two adhere, blood-vessels pass from one to the

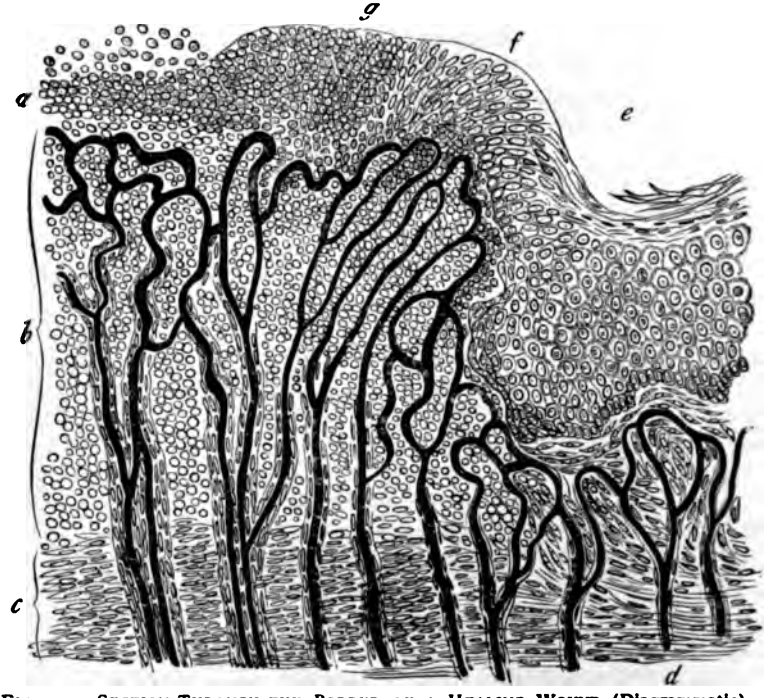

FIG. 194.—SECTION THROUGH THE BORDER OF A HEALING WOUND (Diagrammatic).—(*Rindfleisch.*) × 300 diameters.

a. Surface of ulcer. *b*. Granulation tissue composed of embryonic tissue with the capillary loops developed from the vessels below. *c*. Later stage in the development of the granulation into spindle-cell elements; young cicatricial tissue that is older at *d*. *e*, *f*, *g*. The epithelium spreading over the surface of the healing area.

other, and cicatrization occurs, exactly as already described. The final cicatrization and obliteration of an abscess cavity is secured in this manner. After the evacuation of the pus and the destruction of the bacteria the collapsed walls, coming in contact, unite. It was once considered that union under a scab represented another form of healing, but it is now recognized that granulation and skinning over by epithelium, as already

described, occur. It is not, therefore, a distinct process, but merely a form or combination of some of the foregoing.

A close examination of the forms of repair as just given will show a distinct resemblance of each to all the others; the difference, so striking clinically, is far less marked when we come to investigate the essential changes through which each must pass. In all there is the same preparation for repair, usually effected through the activity of phagocytes. Following or accompanying this, proliferation of preexisting elements and probably certain leukocytes lead to the development of fibroblasts, through the presence of which final cicatrization is brought about. Even the epithelial regeneration is not essentially anything out of the common, as wherever the skin has been wounded, whether the line of injury is microscopic or the surface involved large, proliferation and extension from the margin must be the only normal method of covering the young connective tissue.

Regeneration.—Repair may occur without regeneration. Thus, muscle may be repaired by fibrous tissue, the scar joining the severed ends of the muscle. It does not seem, however, that new muscle is produced. With regard to nerve and bone, this is different; repair terminates in regeneration, and new tissue may be produced that is identical with the original tissue. Regeneration occurs in but few tissues; nerve and bone are the best examples. Repair seems possible in almost any tissue, but such repaired tissue may be, in part at least, functionally inactive, because regeneration has not been complete. Thus, a large cicatrix upon the skin does not contain sweat-glands or hair follicles, and, while it protects the subcutaneous tissues, it performs none of the special functions of the skin. Destroyed kidney tissue may be followed by repair, but apparently not by regeneration.

Many authorities regard regeneration and repair as essentially identical processes; thus, when repair terminates in the formation of fibrous tissue, they say it is regeneration of the fibrous tissue. No one doubts the regeneration of fibrous tissue, but when a large area of the skin or a considerable volume of an organ is converted into fibrous tissue, with the total disappearance of every other structure but the fibrous tissue, it certainly is not correct to say that the organ is regenerated, and the enormous increase in fibrous tissue amounts to something more than the mere regeneration of that element. Repair, as described here, is synonymous with regeneration of the fibrous tissue described by other writers. Regeneration, as already defined, implies the production of new elements structurally and functionally allied to, if not identical with, the destroyed tissue that they replace.

CHAPTER VII.

TUMORS.

The word *tumor*, which means *swelling*, has been variously applied in medical literature. Some writers evidently include among the tumors cellular collections clearly of inflammatory origin; to such aggregations of cells is given the name inflammatory tumors, granulation tumors, etc. The tendency at present is to exclude all such masses and restrict the term tumor to—(1) neoplasms; (2) cysts.

NEOPLASMS.

A **neoplasm** is a pathologic new growth that has a tendency to persist or to increase independently of the structure in which it lies, and that is functionally inactive. A tumor, therefore, differs from an *inflammatory enlargement* by its tendency to persist and to enlarge, while inflammatory new formations tend to disappear or to reproduce the tissue of their matrix. Besides, inflammation has marked clinical phenomena, and not infrequently an assignable exciting cause.

A *hypertrophy* differs from a tumor in the fact that it is the result of increased physiologic demands or of a local nutritive change, and that it tends to subside after the withdrawal of the exciting cause. Also, as a rule, hypertrophy does not destroy the natural contour of a part, while a tumor does. Hypertrophy is associated with increased functional power.

General Considerations.—For purposes of clinical description and pathologic study certain terms are used in connection with tumors with which the student should be familiar. In studying tumors for either diagnostic or pathologic purposes there should always be a definite routine in the method of examination, as has already been insisted upon when considering postmortems. The following order is commended: (1) Describe the tumor; (2) its relation to surrounding tissue and organs; (3) the history of the tumor; (4) the history of the patient. In purely clinical studies it is common to begin with the history of the patient, and the foregoing order may be reversed without affecting its usefulness.

1. In describing the tumor the following points may be of aid in diagnosis, and ought to be developed in the history: (*a*) Its *situation*, superficial or deep, on epithelial or connective-tissue surfaces, or within a structure composed of one or both tissues; this includes the organ involved. (*b*) The *conformation* of the tumor: Is it globular, flat, bossed, pendulous, pedunculated, pyriform, conic, excrescent, polypoid, dendritic, sessile, cauliflower, tuberous, lobulated, fungoid, etc.? (*c*) The *size* of a tumor may be approximately estimated before the tumor is removed from the body. After removal accurate measurements should be made and the mass should be weighed. (*d*) *Number:* Is the tumor single—that is, solitary—or is it multiple? If multiple, was it so from the beginning, or was one tumor followed by a succession of others? Are all the tumors apparently alike, having the same conformation, consistency, and similar location? (*e*) *Consistence:* Some tumors are so soft that they fluctuate; others are *semisolid*, *gelatinoid*, *solid*, *hard*, or even *eburnated*. (*f*) *Color:* This includes the color of the overlying structures. The tissue covering a tumor may be normal or inflamed; it may contain tortuous veins; it may be edematous, or even pigmented; it may be so vascular that the color is of a blood tint, either pink or red, or, in some instances, cyanotic. (*g*) The *mobility* of the tumor: Is the tumor movable in the tissue that surrounds it? Is it movable only with the organ involved, or has the tumor, as well as the organ involved, become attached to adjacent tissue? (*h*) *Sensibility:* Is the tumor painful, tender, sensitive to changes in temperature or to other atmospheric conditions? Is the pain or tenderness constant, remittent, or intermittent?

2. The *influence of the tumor, if any, upon surrounding structures:* Are they involved, inflamed, edematous, sensitive, or anesthetic?

3. The *history of the growth:* How long has the tumor persisted? Is it growing rapidly or slowly? Has its growth been constant or intermittent? Is its growth influenced by any of the functions of the body? (For example, some tumors in women enlarge during menstruation.) What *pathologic processes*, if any, is the tumor undergoing? Is there evidence of inflammation, gangrene, cyst formation, suppuration, infiltration, or of degenerative processes?

4. *History of the patient—Age:* Some tumors appear in the young, others are more frequent in middle life, and some occur in the old. *Sex:* Some tumors are more frequent in the male; others, in the female. Carcinoma of the male breast occurs in

about one per cent. of all cases of mammary cancer. *Social condition:* Married or single. *Occupation:* Certain tumors have long been recognized as frequently associated with given occupations: *e. g.*, chimney-sweep's cancer. *Habits:* Some tumors are dependent, apparently,—to a certain extent, at least,—upon given habits: *e. g.*, smokers' cancer. *Heredity:* There is reason to believe that in some tumors inheritance may play a part. Has the *general nutrition of the patient* been influenced in any way? and is the influence purely mechanical, such as may result from the weight of the tumor, or is it attributable to the position? Have ulceration or infectious processes modified general nutrition? In the absence of any other explanation, it may be inferred that the tumor itself has been prejudicial to the patient's health.

Previous history of the organ or tissue involved: Is there a history of injury or inflammation, such as might occur in the breast during lactation? Has there been any *previous disease of the gland or structure involved*, such as eczema?

Causes.—It is not improbable that different tumors arise as a result of the action of various causes. As, however, we know very little concerning the exact cause of any particular tumor, certain general considerations are permissible. The older theories, attributing the occurrence of tumors to alterations in the humors of the body, particularly of the blood, and similar hypotheses, may be at once discarded. The following hypotheses are deserving of consideration:

1. *The Inclusion Theory of Cohnheim.*—This theory is based upon the supposition that, during embryonic development and the specialization of the cells entering into the formation of organs and adult tissues, more embryonic elements are produced than are necessary, and that these cellular elements become quiescent in the tissues, where they may remain, constituting embryonic "rests" or "remnants," from which, later, tumor formation takes place. Such embryonic rests or remnants would be exceedingly likely to occur where developmental processes are complex, as, for example, where different forms of epithelium join. Such points of tumor election undoubtedly occur, as is shown by the development of cancer at the various orifices of the body and at points of epithelial transition, such as the lip, cervix uteri, etc. This theory also explains to advantage the occurrence of chondroid tumors in or from bone, and of melanotic sarcomata from quiescent pigmented cells in moles, and affords a most acceptable explanation for the development of dermoid cysts. The theory, however, is wanting in several

ways. In the first place, admitting the occurrence of these remnants, it would appear that a further etiologic factor is necessary in order to stimulate them to renewed activity. Another objection is afforded by the fact that many localities in which complex developmental processes occur, such as the heart and the nervous system, are singularly free from tumors, and that when they do occur in such tissues, they are not commonly situated at points at which the complexity of development is most marked. Epithelial rests are sometimes demonstrable, and yet no tumor formation occurs. The occurrence of tumors as the result of trauma (to be considered later) is not fully consistent with this theory.

2. *Injury and inflammation* appear to be, in a certain percentage of tumors, important etiologic factors. Persistent or long-continued irritation seems to favor the development of tumors belonging to the epithelial group. As examples of such tumors the following may be mentioned: Carcinoma of the scrotum in chimney-sweeps; epithelioma of the arm in workers with paraffin and tar; smokers' cancer of the lip or tongue and cancer of the tongue apparently due to injury by a carious tooth; and epithelioma originating in the margins of chronic ulcerative processes. Among the nonmalignant epithelial tumors the development of which may appear to be favored by injury or irritation may be cited the papillomatous masses that occur, apparently as the result of irritation due to the accumulations of irritating discharges, particularly around the anus and external genital organs, when the parts are not kept properly cleansed. Sarcoma following fracture or injury of bone, and fibroneuromata of the severed ends of nerves after amputation, may be mentioned as connective-tissue tumors offering strong support to this theory. The occurrence of tumors at points particularly liable to injury is another argument in its favor.

Numerous objections have been made to the acceptance of this theory. In about eighty-five per cent. of the cases no history of injury can be obtained. On the other hand, the frequency with which injuries are received is not at all in proportion to the total number of tumors occurring. Parts particularly subject to injury, such as the hands and feet, are not commonly affected, and the nipple, which is frequently injured, is rarely the seat of a tumor.

3. *Parasitic Influence.*—The germ theory has been invoked to explain the formation of tumors, particularly the malignant tumors, in which metastases are conspicuous. By some the essential parasitic body is believed to be an animal parasite

belonging to the protozoa and resembling, if not identical with, the coccidia already described. (See p. 193.) Others believe that the infecting body is a vegetable organism belonging to the blastomycetes. In further support of the parasitic origin of tumors the demonstrable autoinoculability of cancer is adduced. Thus, it has been shown that cancer of one labium may attack the point of contact upon the opposite labium; cancer of the cervix may attack the contiguous vaginal vault; and cancer reaching the peritoneal surface may show a similar inoculability. It may be said at this point that such inoculability may be an evidence of grafting, just as epithelial cells may be grafted from place to place without of necessity invoking the intervention of any parasite. A similar explanation is offered with regard to the grafting of cancer from one animal to another. The inoculation of tumors believed to be sarcomata, and occurring on the genitalia of dogs, is believed by some to be an evidence of the inoculability of sarcomata. Others maintain that the tumor in question is not a sarcoma, but that it belongs to that group of inflammatory embryonic cellular collections not easily differentiated from round-cell sarcoma.

4. Parasitism of Cells.—It is not impossible that normal cellular elements may take on a certain parasite-like property that, in the presence of reduced resistance afforded by other elements, permits of their extension beyond normal limits. Thus, in cancer cellular elements that we believe to be of epithelial origin are found abundantly infiltrating connective tissues. Normally, epithelium does not so extend, nor, in most instances, even when introduced experimentally, does it acquire any such property. Should further experiment show that conditions may arise under which epithelium can acquire or manifest the faculty of intraconnective-tissue growth, without the intervention of any other factor, we may assume that the manifestation of this parasite-like character leads to the development of cancer.

The foregoing brief consideration of the most plausible reasons advanced to explain neoplastic growths indicates our ignorance of the essential etiologic factor in tumor formation. There are, however, certain predisposing elements worthy of consideration. Some of the conditions previously considered may be active only in this way. Trauma and inflammation may predispose to tumor formation, just as they predispose to infection, and long-continued irritation or prolonged ulceration may act only as predisposing elements. With regard to age, it may be said, in a general way, that physiologic activity favors the development of sarcoma, while senescence, or physiologic decline, predisposes to the

occurrence of cancer (Da Costa). The influence of inheritance can not be entirely ignored, although it is probably slight.

Neoplasms are subject to two general laws:

1. **Muller's Law.**—*The tissue that forms the tumor has its type in a tissue of the organism, either adult or embryonic.* By this is meant that, no matter what the cellular elements of a tumor may be, such elements occur as normal structures in the adult tissues or in the tissues of the embryo at some period of its development.

2. **Virchow's Law.**—*The cellular elements of a tumor are derived from the preexisting cells of the organism.* Virchow adds that they are derived from the cells of the connective tissue—a view not to be fully accepted.

By the acceptance of these two laws we arrive at the fact that tumors spring from structures once normal, and represent, when fully developed, tissues that were normal; in other words, tumors are not importations into our bodies, but, like all other morbid processes, are perversions of normal cellular activity.

Tumors, in a general way, obey the laws that regulate normal tissue, yet to some extent they live independently of the surrounding tissue. They usually possess their own circulation, and disseminate and proliferate at the expense of the adjacent tissue. While the patient may show every evidence of failing nutrition, and the adult and fully formed tissues of the body are undergoing progressive wasting, the tumor cells may not lessen in the least the rapidity of their growth.

Tumors are said to enlarge or to extend either by (*a*) **interstitial growth** or by (*b*) **dissemination.** By the former is meant that the growth within the tumor is uniform; that it increases in size by proliferation of its cells, without any dislodgment except that incident to one cell pushing another during the process of multiplication. Such tumors are likely to form capsules, the **capsule** developing either as a part of the tumor cells or by condensation of the surrounding tissue. The simple nonmalignant tumors may have capsules formed in either of the two ways indicated, but the malignant tumors are less likely to have anything like a capsule, by reason of the fact that they grow largely by dissemination.

(*b*) **Growth by dissemination** is said to be—(1) **growth by infiltration**; (2) **growth by metastasis.**

1. **Local dissemination** or **infiltration** is an extension of the tumor into the surrounding tissue; this usually occurs by the entrance of the tumor cells into the lymph-spaces. Tumors growing by infiltration have no sharply defined border, and are, therefore, without any capsule, thus rendering the surgeon

unable to determine definitely how far from the neoplasm it is necessary to keep in order to remove all of the tumor tissue.

2. Metastasis.—When, as just indicated, the tumor cells infiltrate the primitive lymph-spaces, it will be seen how easy it is for such infiltrated cells to be caught in the lymph stream and carried to the glands into which the lymphatics of the area involved empty; such extension is most common in cancers, although it may occur in sarcoma, and is known as **metastasis by the lymph stream.**

Metastasis by the Blood.—In certain tumors, particularly in sarcomata, the walls of the blood-vessels are poorly formed—indeed, nothing structurally comparable to the normal wall may be demonstrable; the blood traversing such tumors passes through what may be called sluiceways, the walls of which are not uncommonly formed entirely of tumor cells. These cells may drop off into the blood stream and be carried along as emboli (neoplastic emboli), reproducing the tumor wherever they lodge. Again, a tumor may infiltrate the wall of the blood-vessel and project into its interior, and small fragments, breaking off, may be carried to distant parts. The walls of the veins being thinner than those of the arteries, infiltration is rendered easier, and the circulatory conditions make the consequences more disastrous. Neoplastic emboli formed by penetration of the femoral artery can be carried only to the structures of that limb; if, however, the emboli be thrown into the femoral vein, their next point of lodgment would probably be the lung.

Pigmentation occurring in tumors may be due to hemorrhage within the tumor and to the breaking down of blood coloring-matter, or it may be due to the fact that the tumor produces a pigment, such as is seen in the chloroma, melanotic sarcoma, and a few other tumors. It may also be due to the development of certain bacteria, particularly if the tumor be ulcerated.

Classification.—Clinically, tumors are said to be (*a*) **benign** or (*b*) **malignant.** By the former is meant that the tumor of itself does not necessarily involve danger to life, while the latter implies that, if let alone, the tumor will eventually prove fatal. A tumor ordinarily innocent or benign may destroy life simply by its location: for example, a fibrous tumor growing on the inside of the skull. This, however, does not justify our placing fibrous tumors with the malignant neoplasms, as the fact that it proves fatal, in the particular instance cited, is what Park has termed "malignancy by accident of location."

At one time it was quite the custom for clinicians to classify tumors according to some symptom or peculiarity of shape.

As examples of this, we have scirrhus, for hard, and encephaloid, for soft; again, bleeding tumors, when fungoid, all came under the one head, "fungus hæmatoides." No fully satisfactory classification of tumors can be made at present; when we become familiar with their etiology, it is probable that more may be accomplished. The extension of our knowledge as to the minute structure of tumors has led to a classification based upon their morbid histology and histogenesis.

Classification Based on Histogenesis.—Granting the correctness of the law of Müller, a tentative classification is possible, based upon the resemblance of tumors to the normal tissues, either adult or embryonic. All tissues spring from one of two types: (*1*) *Epithelium;* (*2*) *connective tissue.* Tracing these back to the blastodermic layers, they are developed as follows:

(*1*) *Epithelium*, from the epiblastic and hypoblastic layers (or outer and inner layers) of the blastoderm. (*2*) *Connective tissue*, from the mesoblast (or middle layer) of the blastoderm. All neoplasms spring from one of these two types, each type of tissue having two varieties:

(1) **Epithelium**: (*a*) *Adult* or *typical;* (*b*) *embryonic* or *atypical.* (2) **Connective tissue**: (*a*) *Adult* or *typical;* (*b*) *embryonic* or *atypical.*

By *adult* or *typical* tumors is meant those having their type in the adult body; clinically, these are *benign.*

Embryonic or *atypical* tumors are composed of cellular elements resembling those found in the embryo at some stage of its development; clinically, such tumors are *malignant.*

EPITHELIAL TUMORS.

ADULT EPITHELIAL TUMORS.

I. Papilloma.—These growths are formed from cutaneous and mucous papillæ, and consist of a fibrous stroma, or stem, containing blood-vessels and lymphatics, and possessing an epithelial investment. The epithelium is of the kind normal in that particular situation. The histologic structure of a papilloma is the same as that of the ordinary papilla, and consists of a basis of connective tissue, richly cellular, from which project toward the surface numerous papillary processes, each process supporting blood-vessels that end in a capillary loop, the whole being enveloped in a covering of epithelium.

The papillæ vary in length: in the ordinary wart they are

short; in the *villous papilloma* they appear as long, delicate fibrils, giving off secondary and tertiary shoots.

On the skin the epithelial covering is thick, hard, and stratified, and actually binds the papillæ into a solid mass; on mucous membranes the slender vascular processes are covered with very delicate and easily lacerated epithelium.

Site.—Papilloma may appear anywhere on the skin or mucous membrane; as a rule, they grow from, and closely imitate, pre-existing papillæ. They rarely occur where no papillæ exist; in such rare cases they spring directly from the subepithelial connective tissue—this is the case in the *stomach* and *larynx*.

FIG. 195.—PAPILLOMA.—(*Gould.*)

Clinical Characteristics. — Clinically, warts are benign, or innocent. They may occur at any age; may be single or multiple; may disappear without any operative interference: this is especially true of multiple warts. When occurring on mucous surfaces, they are highly vascular, and, owing to their thin epithelial covering, cause much trouble, and even death, by bleeding. This is especially true in the bladder and in the urethral orifice. In the young, warts are occasionally transformed into sarcomata; in advanced life warts and warty surfaces (ichthyosis linguæ) may be converted into cancer.

Varieties.—(*1*) *Skin warts;* (*2*) *villous warts;* (*3*) *intracystic warts.*

1. Skin Warts.—(See Fig. 195.) Skin warts are overgrown papillæ, and on section the epithelium will be found to pass from one papilla to another in an unbroken line without invading the fibrous framework. They vary in size, and may become mottled with black pigment (melanotic). Cutaneous warts may be single or multiple, and may disappear in one area and appear in another, thus leading the laity to believe them migratory. Ordinarily, the cutaneous papilloma appears as a hard, abruptly elevated mass, apparently of epithelium, presenting an irregular or "warty" surface, usually divided by deep fissures. On section, the relation between the stroma and the epithelium may be seen even with the naked eye.

2. Villous Warts.—These commonly spring from the mucous membrane, usually of the bladder, and occasionally of the renal pelvis; the condition is termed *villous disease.* The general appearance of the long, branching, feathery tufts resembles that of

the delicate chorionic villi; structurally, the villi consist of a connective-tissue core traversed by delicate blood-vessels, the whole being surmounted by epithelium. They may be *single* or *multiple*, sessile or pedunculated. The tearing off of small villi may occasion hemorrhage, which, with frequent recurrence, gives rise to profound anemia. The size of the villous mass often bears no relation to the severity of the hemorrhage; the writer has examined, at autopsy, a fatal case in which the papillomatous mass was not larger than a grain of wheat. The detachment of the villi is usually brought about by their being forced, during the last stage of urination, into the urethra, where fimbriæ are caught; distention of the bladder pulls upon the incarcerated

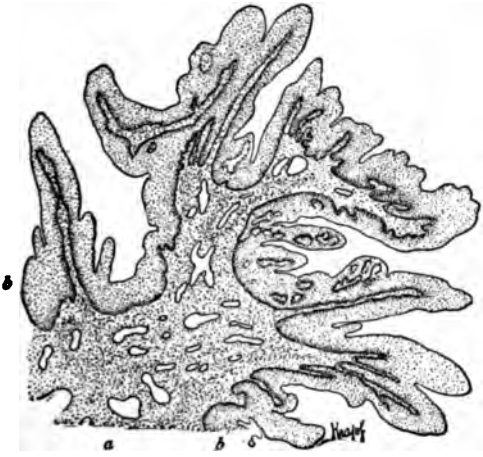

FIG. 196.—PAPILLOMA WITH TENDENCY TOWARD VILLOUS FORMATION.—(*Schmaus.*)
a. Connective-tissue basis containing numerous blood-vessels. *b*, *b*. Epithelial covering.

villi, breaking them off, and thereby inducing hemorrhage. Carcinomatous transformation of vesical papilloma occurs.

3. Intracystic Warts.—These may occur within almost any cyst cavity lined by epithelium, more especially those cysts formed in glands: *e. g.*, mammary cysts, thyroid cysts. In cysts formed in the mammary gland, particularly in those cysts arising during the growth of fibrous tumors of the breast, the wall may be formed by a papillomatous outgrowth. Tumors composed of papillomatous masses in the interior of dilated galactophorous ducts or mammary acini are spoken of as *intracanalicular papillomata*. Sometimes the cyst is said to be papillomatous. In many instances it may be quite impossible to determine whether the cyst

preceded the papillary growth or whether the reverse was the case. Examination of a number of such cysts usually shows that the papillomatous growth is evidently a secondary process. Occasionally, the cyst may be distended with the papillary masses, the fluid, probably present at some time, having entirely disappeared. Cysts containing such papillomatous masses are sometimes seen in the liver. The villous outgrowth resembles that of villous papilloma, and the epithelial covering is usually the same as that of the cyst wall; it may be cylindric, tall or flat, and even ciliated. The size of such masses varies within wide limits, and the fact that their presence is at times unsuspected would lead one to regard them as sources of no danger. Occasionally, however, scirrhus of the breast follows or is associated with such masses.

II. Adenoma.—An adenoma is a tumor constructed upon the type of a gland. Adenomata are of slow growth, and are believed to have their origin in some quiescent, congenitally displaced rudiment; their ducts do not communicate with the normal gland nor do their acini elaborate a secretion; they are, as a rule, completely encapsulated, thus distinguishing them from localized hypertrophies. Clinically, they are benign. The secondary changes to which they are liable are fatty degeneration of the epithelium, dilatation of the saccules and tubules into cysts, and mucoid softening. As adenomata contain both connective-tissue cells and epithelial cells, transformation into sarcoma and into carcinoma is possible; the former is more frequent in the young, and the latter in the aged.

Site.—They may develop in any glandular structure or in any tissue containing glandular structure. The chief species of adenoma are: Mammary, sebaceous, thyroid, prostatic, parotid, hepatic, renal, ovarian, testicular, gastric, Fallopian, and uterine.

Varieties.—(*1*) *Acinous*; (*2*) *tubular.*

1. Acinous Adenoma.—This variety consists of numerous saccules or acini lined with small epithelial cells, which are often two or three layers deep. The acini communicate with one another and are grouped together, being separated by a connective-tissue matrix in which are situated the blood-vessels. The connective tissue or fibrous stroma varies in amount. Adenoma of the breast is generally seen in young girls at about the age of puberty. The tumor is usually bossed or lobulated, irregular in conformation, and encapsulated. Acinous adenoma is rare, but two cases having come under the author's observation among the hundreds of tumors sent to the laboratory. Fibromata showing more or less glandular structure are not uncommon,

and are called **fibroadenomata.** It is often quite impossible to determine whether the gland structure present is newly formed or merely the incarcerated normal breast tissue.

2. Tubular Adenoma.—This variety is very common in mucous membranes possessing tubular glands. Tubular adenomata are usually soft, slightly translucent, and somewhat vascular. The tubes are lined with cylindric-cell epithelium. On section, when cut transversely, the tubes appear as circles, with a

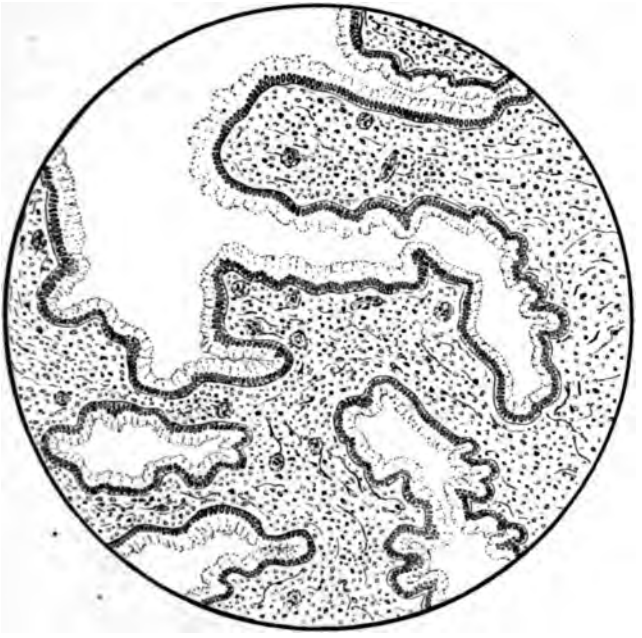

FIG. 197.—ADENOMA OF THE CERVIX UTERI.—(*From a specimen sent to the author by Dr. E. Q. Thornton.*)

The gross specimen was a strawberry-like, pear-shaped mass, 2.5 cm. in length, and attached by a pedicle to the anterior lip of the cervix uteri just at the margin of the os. The tissue was fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. Drawn from ¼-inch obj., ½-inch oc. The irregularly formed gland tubules, lined by tall cylindric epithelium, are well shown.

central lumen and a border of regular cylindric epithelial cells. When cut longitudinally, they often show lateral buds, or even bifurcations, terminating, at one end, in the mucous membrane, where they open, at the other end in blind sacs extending to varying depths; the tubes may be so closely packed together as to show but little fibrous stroma; the cylindric cells lining the tubes are usually two or three times as long as normal. This

variety of adenoma is prone to undergo malignant transformation, many of the cancers of the rectum and uterus arising from this tumor.

Rectal adenomata are most frequently seen in children, although they may occur at any age. They are strawberry-like or raspberry-like tumors, rarely over one or two centimeters in diameter, although the author has had the opportunity to examine such a tumor that was six centimeters in its longest diameter. Most observers have found them multiple; this has not been the author's experience. The glandular structure imitated is the gland of Lieberkühn. The tendency to transformation into carcinoma (cylindric-cell epithelioma) is remarkable; the author has never known a tubular adenoma to persist for any great length of time and escape the change. The same is true of a very similar tumor—*adenoma of the cervix uteri.* The great difficulty found in differentiating, histologically, between this tumor and cylindric-cell cancer will be referred to when considering the cancer.

III. Neuroma.*—A *neuroma* is a tumor consisting almost entirely of nerve tissue; pure neuromata are among the rarest of new growths. The term "false neuroma" has been applied to many growths found in connection with nerves; under this head should be classed the fibrous, myxomatous, and gummatous tumors found on, in, or around nerves. The plexiform neuroma is composed of a series of nodules along the course of a nerve or in a nerve plexus; at one time this was thought to be a true neuroma; at present it is believed that the new tissue is essentially fibrous, and hence the tumor belongs among the false neuromata or, properly, among the fibromata of nerves. The small multiple fibromata or neuromata of superficial nerves are usually hereditary. The amputation neuromata—which consist usually of fibrous tissue, but which may contain partially regenerated nerve-fibers—form bulbous masses at the cut end of nerves in stumps after amputation, and are intimately connected with the cicatricial tissue of the stump; they are usually painful.

Varieties of Neuroma.—Many tumors found in connection with the nervous system have been shown, with the later improved methods, to contain a quantity of nervous tissue insufficient to justify their special consideration as neoplasms composed of that

* The exact oncologic position of neoplasms arising from the central nervous system is still a matter not fully determined. Recent researches bearing upon the embryology and histology of the nervous system indicate that neuromata and gliomata may be, for the present, considered with neoplasms of epithelial origin.

structure. In theory all true neuromata could be classed under one of three heads: (1) Tumors composed of or containing ganglion cells—*ganglionic neuromata;* (2) tumors made up or composed largely of newly developed medullated fibers—*myelinic neuromata;* (3) tumors composed of or containing evidently newly formed nonmedullated nerve-fibers—*amyelinic neuromata.*

IV. Glioma (*Gluey Tumor*, Virchow).—The sustentacular tissue of the nervous system, according to recent observations, is a derivative of the ectoderm, and, therefore, tumors arising from or composed of such elements should be classified with the neoplasms of epithelial origin. Gliomata are tumors apparently derived from the sustaining tissue of the central nervous system, —the neuroglia,—and are composed of glia cells more or less closely imitating the normal elements. As the glia cell differs at various stages in its development, the adult cell scarcely more than resembling its embryologic ancestor, so differ the cellular elements that enter into the formation of gliomata. In some instances the tumor is made up of cells showing a relatively small number of fibers, comparatively large in size; other tumors are particularly rich in fibers. With regard to the size of the cell, it may be small, large, or even approaching the size of a giant-cell. Again, tumors occur that appear to be appropriately classed with the gliomata, and in which the cells more closely resemble ependyma cells. For this class of tumors Flexner has proposed the name *ependyma-cell glioma.* Gliomata are sometimes found containing cellular elements indistinguishable from the cells found in small round-cell sarcoma, and, unfortunately, to such tumors the name **gliosarcoma** has been given. Tumors of this type are most frequent in the eye, apparently originating from the retina. That some of them are true sarcomata is indicated by their occurrence in the young (children from two to six years), by their extension in continuous structures, such as the optic nerve, and by the involvement of the contiguous tissues; not uncommonly they produce fungoid masses, which project from the orbit; they recur after removal. Gliomata of the brain do not involve the membranes; sarcomata do. Glioma contains, in nearly all instances, medullated nerve-fibers; sarcoma rarely. (For the stain and differentiation of glia elements see article on Central Nervous System, in part III.)

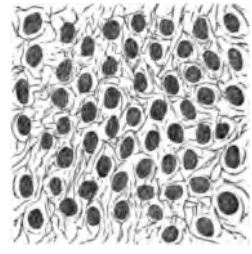

FIG. 198.—GLIOMA.—(*Gould.*)

Gliomata appear as more or less circumscribed or slightly diffuse tumors of the central nervous system. As already indicated, their consistency is largely dependent upon the character of the cellular elements that enter into their formation. Occasionally, the tumor may be so soft that it can be handled only with difficulty; in other instances it is firm, and even elastic. The color is dependent upon the amount of blood present and upon the presence or absence of hemorrhage or of degenerative change. Areas of softening or even of cyst formation are occasionally present. Sometimes these cysts show an epithelial lining, the cells of which resemble those forming the wall of the central canal. Commonly, but a single tumor is present; in rare instances, however, the tumor may be primarily multiple, and in still other cases tumors evidently of different ages may be found. In a pure glioma metastasis apparently does not occur. When rapid growth and metastasis are present, the tumor is probably a sarcoma.

Site.—Brain and cord; optic nerve and retina; olfactory lobe.

EMBRYONIC EPITHELIAL TUMORS.

Carcinomata, or cancers, are embryonic or atypical neoplasms that do not have their type in adult epithelial structures, but revert to the embryo for their prototype. They always develop from the *epithelial* cell, which cell becomes abnormal in form and, if growing in glands, fills up the lumen of the gland's tubule, acinus, etc., penetrating the basement or limiting membrane, and infiltrating the lymph-spaces of the connective tissue. Carcinomata are composed, for the most part, of epithelial cells growing out of place.

Histology.—In carcinoma two essential elements must be described: (1) the *epithelial cells;* (2) the *stroma,* which bounds the space in which the epithelial cells lie, the space being known as the *alveolus.*

Cells.—The cells are characterized by every diversity of outline; they may be round, oval, squamous, fusiform, cylindric, or caudate, and with prominent nuclei and nucleoli. The nuclei may be single or multiple, but are always large and prominent. The variation in form of the cell is due to the pressure to which it is subjected within the alveolus and to the shape of the cell from which the cancer arose. The cells are loosely nested in the alveoli, and do not attach themselves to the fibrous stroma.

Fibrous Stroma.—The amount of fibrous stroma varies: it consists of distinctly fibrillated tissue, arranged so as to form the

alveoli. The alveoli communicate with one another and form a continuous cavernous system, within which the epithelial cells are found.

The character of the stroma depends largely on the rate of growth. If rapid, it will contain some round and spindle-shaped cells ; if the growth has been slow, or has ceased altogether, the tissue will contain few or no recent or round cells, and will be more dense and fibrous in character. The latter is the most common condition in scirrhus, the former in encephaloid cancer. The stroma not uncommonly contains a varying number of unstriped muscle-cells, or other histologic elements of the tissue in which the carcinoma is developing. The stroma of uterine cancer is particularly rich in involuntary muscle-fibers, and cancer involving bone may show more or less osseous structure within the stroma. Situated in this stroma are the blood-vessels, which are limited to the stroma, and do not pass into the alveoli or communicate with epithelial masses ; they have distinct walls that are not infrequently thickened. The lymphatics communicate freely with the alveoli, which fact accounts for the frequency of infection of lymphatic glands. It is through these channels that carcinoma spreads. The alveoli were originally lymph-spaces, and therefore communicated directly with the primitive lymphatic ducts draining the area. This communication is not interfered with by the growth of the cancer, but is probably facilitated by the distention of the primitive lymph-spaces by the epithelial cells. As already indicated, the epithelium may readily pass onward, entering the primitive lymphatic ducts, and later the larger ducts, and eventually the gland or gland chain lying between the carcinomatous area and the lymphatic duct that empties into the vein. The extension of cancer along the course of nerves—as, for example, the inferior dental nerve—or along vascular trunks is probably due to the presence of lymph paths that follow the course of the vessel or nerve sheath. By some authors, however, it is considered as a distinct form or method of cancerous extension.

Clinical Characteristics.—As a rule, carcinoma occurs after the age of thirty-five. Over fifty per cent. of all cancerous growths develop after the forty-fifth year. The age of the patient is not so important as the evident age of the structures involved. Thus, the author has seen a well-formed scirrhus of the breast in a patient of twenty-two. The mamma involved, as well as its fellow of the opposite side, showed distinct atrophic changes. The diseased mamma was removed, the tumor did not return, and the patient passed the menopause at thirty. Such instances,

while apparently exceptions to the rule that cancer occurs in middle life, are only apparent and not true exceptions. Such individuals are aging prematurely, and in the diagnosis of cancer such factors must be taken into consideration. The growth is usually primarily single. Generally, the tumor is hard. The so-called soft cancers are those that have undergone some secondary change, as fatty or colloid, or are made up of epithelium in excess, as the encephaloid. Cancers tend to infiltrate adjacent connective tissues. There is usually a central tumor mass, from which processes radiate into the surrounding tissue. The border of the tumor is not sharply defined; the typical connective-tissue and epithelial-tissue tumors, on the other hand, are likely to have well-defined margins, and, in most instances, can be enucleated from the tissues in which they lie. Carcinoma has no capsule and can not be enucleated.

Secondary carcinoma is usually multiple, has a more sharply defined or circumscribed border, and, while it projects into the neighboring tissues, does not tend to infiltrate them with the same rapidity as did the primary tumor; as a rule, the mass is much softer. These characteristics are probably due to the recent and rapid growth of the neoplasm.

Secondary Changes.—The most important are certain forms of degenerative change, among which is fatty degeneration. This depends somewhat on the rate of the growth; the more rapid the growth, the more rapidly this change takes place; hence it is usually most marked in encephaloid cancer. *Colloid degeneration* of the alveolar contents and *myxomatous degeneration* of the connective-tissue stroma are occasionally observed. These processes are particularly marked in carcinomata involving the stomach. *Pigmentation*, or *melanosis* (melanotic cancer), is rare. Calcific deposit, or even true bone formation, may occur; they are, however, quite infrequent. The cysts occasionally formed in cancer arise as the result of liquefaction necrosis or of degenerative changes in the cellular elements, or, probably, in most instances, are dependent upon the presence of cysts prior to the carcinomatous development. The contents of such cysts may be fluid, mucoid, or colloid material, and, in rare instances, they may contain more or less blood; the extravasated blood may undergo degenerative and necrotic changes, leaving little of the normal constituents to be recognized, except the altered brownish pigment. Small areas of hemorrhage into the stroma are not so infrequent, and when ulcerative processes have exposed the surfaces, or when associated necrosis and infection are present,—as in cancers of the uterus and stomach, and oc-

casionally in cancer of the mammary gland,—hemorrhage may be severe and even fatal. The size of the cancer often bears no relation to the amount of hemorrhage, the latter being apparently dependent upon the size of the vessels involved, and possibly, to a less degree, upon the activity of the infective processes.

Various infections occur in carcinomatous tissue. After solution in the continuity of the superficial covering, infection may be marked, and the systemic phenomena of sepsis may interfere with the general nutrition, sometimes demanding operative procedures in cancers the extent of which precludes the possibility of complete removal. The associated infections are usually pyogenic. Numbers of saprophytic organisms may be present. Tuberculous processes, for example, in the esophagus or larynx may become carcinomatous, or an ulcerating carcinoma may become tuberculous. Tuberculosis and associated cancer of the skin have been observed, and lesions apparently primarily syphilitic, have become cancerous. Evidences of gumma formation in cancer are less frequent, if ever present. Distinct abscess formation is infrequent. Necrotic processes, and even extensive gangrene, may at times be observed.

Site.—The presence of epithelium being the essential requisite, any surface, tissue, or organ containing this element may become carcinomatous. To a certain extent the various forms of epithelium seem to influence the occurrence of different varieties of cancer. The cause of this influence will become more evident as we proceed with the consideration of the forms of carcinoma.

Varieties.—(I) *Epithelial carcinoma;* (II) *glandular carcinoma.*

The term epithelioma is used in a broad sense by some writers as referring to all carcinomata. It is here applied to those varieties of carcinoma that usually spring from epithelial surfaces, and is often spoken of as superficial cancer.

I. Epithelioma assumes three types: (*1*) *Squamous;* (*2*) *cylindric-cell;* (*3*) *tubulated.*

1. Squamous Epithelioma.—This variety always grows from surfaces covered by squamous epithelium, either cutaneous or mucous; its epithelial elements closely resemble squamous epithelium; the distortion in shape of the cell is due to the pressure to which it is subjected during its growth. The cells penetrate from the surface epithelium into the lymph-spaces of the connective tissue, and follow those channels that intercommunicate. Occasionally, single isolated epithelial cells may be recognized in the connective tissue of the growth. Transverse sections of the epithelial masses show typical nesting of cells—the so-called *concentric globes* or *epithelial nests.* When these

nests undergo hardening,—a change incident to age and to attempted desquamation,—they are spoken of as "*pearls*," hence the term *pearl epithelioma*. These yellowish spherules, composed of cornified or keratinized epithelium, are commonly microscopic bodies situated within the alveolar contents, and showing a marked affinity for acid dyes, notably for the picric acid stains. In rare instances they may be large enough to be seen with the naked eye. The author possesses one specimen of this kind. The diagnostic importance of such bodies (they were at one time held to be pathognomonic) is lessened by their occurrence in other conditions associated with inflammation of the skin; they are occasionally seen at the margins of ulcerative processes that evidently are not cancers, and are prone to occur at the edges of the granulating tissue around in-

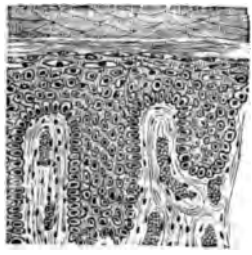

FIG. 199. — SQUAMOUS EPITHELIOMA. — (*Gould.*)

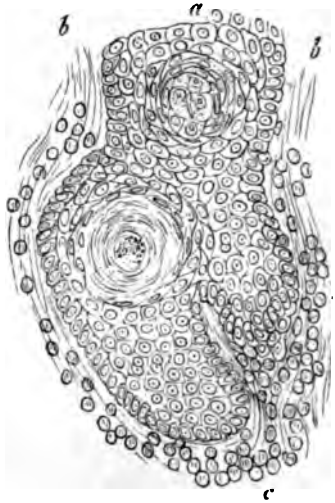

FIG. 200.—SECTION OF A SQUAMOUS EPITHELIOMA.—(*Rindfleisch.*) × 500 diameters.

a. The down-growing epithelium in which are two cell nests or pearls. *b*, *b*. The stroma, in which, at *c*, a few lymphoid cells are to be seen.

growing nails and in onychitis. The fibrous stroma may show some inflammatory infiltration, particularly if the ulceration incident to softening and infection has occurred. It shows little of the alveolar arrangement that characterizes some of the other varieties of carcinoma. The ulceration, which occasionally occurs early, may not be due to inflammatory or infective processes, as is usually the case, but to fatty degeneration of the cells.

The growth usually begins as a small nodule, situated in the connective tissue just under the epithelial layer, with which it is continuous; the skin is not movable over the indurated mass. Not uncommonly the spot of induration may appear to be

in the epithelial layer. As a rule, the overlying epithelium is pushed upward, giving rise to moderate elevation; this indurated elevation may show slight umbilication, due to fatty changes, absorption, and shrinking in its interior, before superficial exfoliation or ulceration occurs. When fully developed, the cancerous surface presents an irregular, ulcerated, warty appearance, exuding from its surface at times a clear, or slightly tinged, or, it may be, an irritating, ichorous fluid. The ulceration occurs in the center, surrounded by an indurated area, beyond which may be firm and distinct nodules. There is often a distinct tendency toward scabbing, particularly when situated on the general cutaneous surface, the lip, and at other mucocutaneous junctions. The scab remains attached for a varying length of time, and then falls off or is removed by the patient; after its removal the underlying cancer, just described, is seen to be slightly larger than before the scab formed. This gradual increase in the size of the cancer, observable after each exfoliation of the scab, is often of diagnostic importance, as is the gradual extension of induration in the tissue beneath. The area of recognizable induration is not the limit of the tumor—a fact always to be borne in mind during its removal. On section, the tumor is firm, and the fibrous stroma may show as white glistening bands. As a rule, there is no hemorrhage; there are few blood-vessels near the surface. The process develops slowly, and glandular involvement may not occur for years, although in rare instances it has been observed within the first year.

Site.—Squamous epithelioma usually occurs at the junction of the skin and the mucous membrane, or where two kinds of epithelium join. It is frequently found on the lower lip, nose, penis, scrotum, vulva, anus, and tongue; less commonly on the gums, palate, tonsils, larynx, pharynx, esophagus, bladder, os uteri, and general cutaneous surface; rarely on the hands and feet.

2. Cylindric-cell Epithelioma (*Adenoid Cancer, Columnar-cell Epithelioma, Malignant Adenoma*).—This variety of cancer is characterized by irregular or tubular cavities, paved with one or more layers of cylindric cells, and separated by a stroma, which may be fibrous, embryonic, or mucoid. In structure it is said to occupy an intermediate position between the simple adenoma and true cancer. The cylindric cells are similar to those that cover certain mucous or glandular cavities, and are always implanted more or less perpendicularly to the wall. The epithelial elements are similar to those of the mucous membrane from which they grow, but differ microscopically from the arrangement in the normal mucosa in the absence of a basement membrane (mem-

brana propria). The slower the growth, the more nearly typical is the attempted gland formation; in rapid growths and recurrences the cells are small and the lumina imperfect.

Cylindric-cell carcinomata are soft, and are often of a gelatinous consistence. On section, they present a soft, watery appearance. The rate of growth varies in different cases, and often within wide

FIG. 201.—CYLINDRIC-CELL CANCER OF THE STOMACH.

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *A*. Drawn from ⅛-inch obj., ¼-inch oc. *B*. Drawn from ⅔-inch obj., ½-inch oc. The upper and right-hand quadrant of the circle shows the fully developed cancerous tissue. The lower portion, just above the letter *B*, shows the beginning production of the gland-like tubules and the extension of the cancerous tissue into the gastric wall. At *C*, and also in other parts of the field, the stroma resembles myxomatous tissue.

limits; it may be rapid or slow—frequently rapid. Glandular involvement, or metastasis, usually occurs early and progresses rapidly. In cylindric-cell cancer of that portion of the alimentary canal drained by the portal vein metastasis to the liver is common. Uterine and other forms of pelvic cancer may be similarly disseminated.

Age.—Cylindric-cell epithelioma, as a rule, occurs earlier than any other variety of epithelioma.

Site.—Rectum (rectal carcinoma may occur very early in life), stomach, uterus, ovary, gall-bladder, liver and biliary passages, and respiratory tract; cylindric-cell cancer may occur in any portion of the intestine.

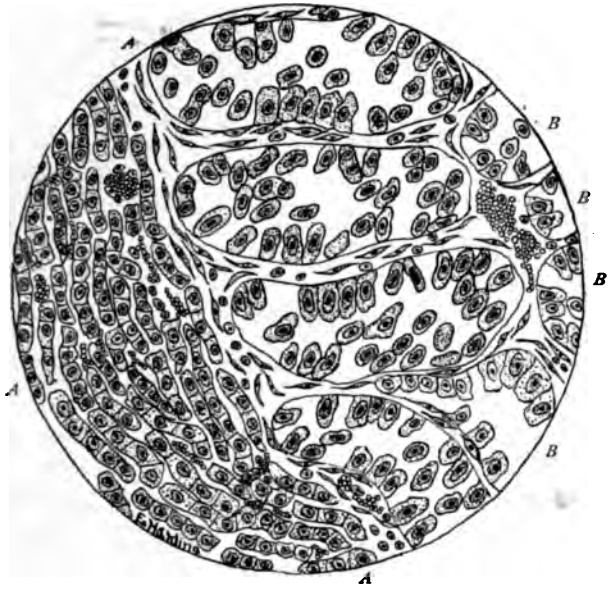

FIG. 202.—SECTION OF CARCINOMA OF THE LIVER.

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with toluidin-blue and eosin, and mounted in balsam. Drawn from ¼-inch obj., ½-inch oc. *A*, *A*, *A*. The liver tissue adjacent to the tumor. The rest of the field consists of three complete alveoli, and parts of five other alveoli. Two of the complete alveoli occupy the central portion of the drawing, while the third alveolus (practically complete) is in the extreme upper portion. The parts of alveoli are indicated by the letters *B*, *B*, *B*, *B*, *B*. About one centimeter inward, and to the left of the second *B* from above, a small area of hemorrhage is to be noticed. A similar but smaller area of hemorrhage is seen just below the lower alveolus. The section was taken from a primary cancer of the liver, which showed, in some areas, a structure closely resembling the cylindric-cell cancer; in other areas the absence of any intra-alveolar arrangement of the cells leads to an encephaloid appearance. It will be noticed that in the alveoli shown there is not the characteristic cylindric arrangement of the cells to be seen in figure 201. At some points, however, there is seen a distinct attempt at such an arrangement. The absence of any capsule, or of any effort at capsule formation, between the tumor and the adjacent liver-tissue is well shown. An illustration showing the gross appearance of this tumor is to be found in the chapter on the Liver, part III.

As secondary growths, this variety of cancer occurs in the lymphatic glands, liver, lungs, and kidney, and in bone. The secondary nodules possess the same characteristics as the primary growth.

The most common forms of degenerative change are mucoid and colloid.

As already remarked, cylindric-cell cancer resembles very closely the tubular adenoma. (See p. 315.) The very close resemblance of the two varieties of tumor has led observers to regard them as possibly identical; the structural difficulty has been concealed by associating with it the clinical phenomena;

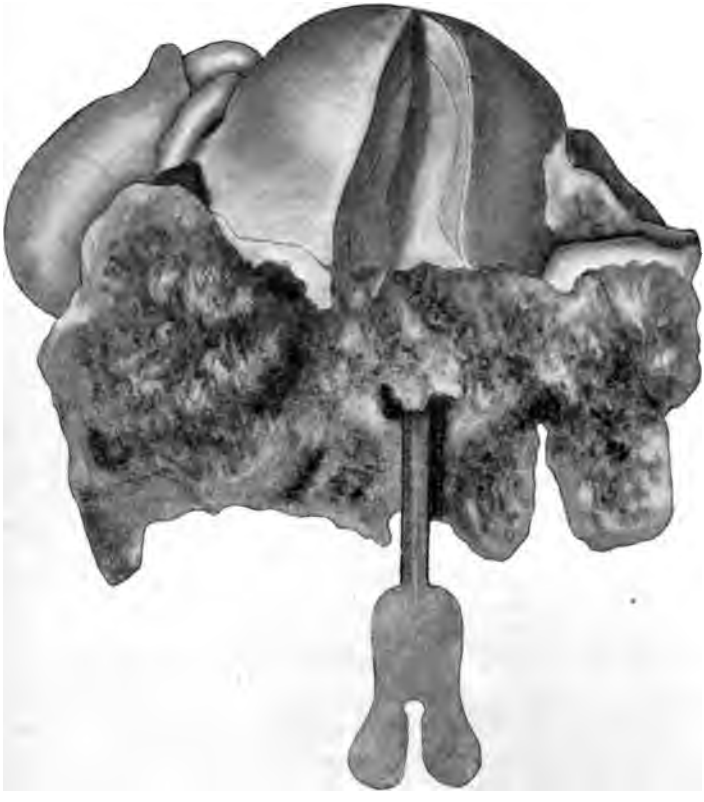

FIG. 203.—CYLINDRIC-CELL EPITHELIOMA OF THE CERVIX UTERI.

The cervix and most of the body of the uterus have been destroyed by the necrotic process. The grooved director, shown in position, passes through a perforation into Douglas' pouch. The ovary shown on the left is much enlarged, and is apparently invaded at its point of attachment to the uterus behind. The vaginal vault and the posterior bladder wall have been destroyed.

thus, we find in the German literature constant reference to simple adenoma and to malignant adenoma, meaning by the former the tubulated adenoma, and by the latter the cylindric-cell cancer at present under consideration. It is evident, clinically, that the two tumors are not identical. The small, strawberry-like polyp

of the rectum, in children, never recurs after removal, and of the many specimens of simple adenoma of the cervix uteri that the author has seen, none has recurred if removed early in life. In tracing the cases of clearly marked cylindric-cell cancer not a single instance has occurred in which recurrence did not take place in the course of time. Sometimes the newly formed tubules are surrounded by a distinct membrana propria; such a tumor must evidently be a simple adenoma. In the typical tubules of the cylindric-cell cancer no basement membrane is ever demonstrable; in the cancer there is a more lawless, purposeless, irregular distribution of the gland-like epithelial cells, and usually a sufficiently prolonged search will show areas so clearly cancerous that the diagnosis can not be doubted. That the simple adenoma may be converted into the cancerous tumor there can be no doubt. Admitting this possibility, we must concede that intermediate structural gradations occur, and that occasionally tumors are found in which, from the examination of a single slide, it is quite impossible to state definitely whether they are simple or malignant. Recognizing that adenoma of this kind is likely to become, without any apparent reason, malignant adenoma, it seems to the author that the method of treatment of such cases is at once simplified—the dangerous character of all doubtful growths of this kind should be admitted, and, in the absence of positive knowledge to the contrary, they should be treated as cancer.

3. **Tubulated Epithelioma** (also variously known as *Rodent Ulcer*, *Tubular Epithelioma*, *Noli me tangere*, *Lupus Exedens*, *Herpes Exedens*, etc.).—This form of epithelioma is composed of irregular pavement epithelium arranged in plugs or cylinders that anastomose with one another and are embedded in a stroma consisting of connective tissue—embryonic, mucoid, or, more commonly, dense and fibrous. When mucoid, it is more likely to undergo further degeneration and to become cystic. The epithelial nests and pearls seen in the squamous epithelioma are absent. In some instances the histologic arrangement resembles scirrhus.

With regard to the gross appearance and development of this tumor, descriptions have been given that evidently include true lupus (cutaneous tuberculosis). The resemblance is often striking, and a microscopic examination is, in most instances, necessary to differentiate between the two conditions. Tubulated epithelioma occurs in the aged; it appears on the mucous surfaces earlier in life than on the cutaneous surfaces. The majority of cases coming under the author's observation have begun on the lower

eyelid. Ulceration appears early, but progresses very slowly, and the process may remain stationary for months, or even for years. The edges of the ulcer are usually elevated, irregular, and indurated. The degree of induration depends largely upon the duration of the process. In old, slowly extending ulceration the induration is more marked than in rapidly progressing lesions. Instances are not infrequent in which partial healing of the ulceration has taken place, and in which, after a variable period of quiescence, extension has been resumed. Sometimes, without any discernible cause, the growth suddenly assumes remarkable activity, and in a comparatively short time shows extensive involvement of adjacent tissues. The author recalls a case in which a tumor developed on the lower eyelid as a small ulceration, ovoid in outline, and, after three years, its diameter did not exceed 0.5 cm. It was excised and its cancerous nature was satisfactorily determined by microscopic examination. Within a year a small recurrent lesion appeared at the site of excision, which, in five years, showed but little tendency toward extension. The tumor then began active growth, and inside of two months had involved the entire lower eyelid and part of the cheek, and had almost entirely destroyed the eye. Excision was again attempted, but seemed to exert but little influence on the rapidity with which the cancer extended.

Glandular involvement is more uncertain in these cases than in any other variety of cancer; in some instances the spread is rapid; in others, slow; in some cases it does not appear at all. When upon the mucous surfaces or upon the eyelid, the growth is frequently rapid.

Site.—The most frequent location is on the face, tongue, general cutaneous surface, intestine, uterus, and ovary. When occurring in the skin, the mass is believed to develop from the sweat-glands, or, possibly, from the hair sheaths.

II. Glandular Carcinoma.—*Varieties.*—(*1*) *Scirrhus;* (*2*) *encephaloid carcinoma.*

1. **Scirrhus** (*Acinous Cancer, Chronic Cancer, Hard Cancer, Fibrous Carcinoma*).—This variety of carcinoma is characterized by the amount and density of its stroma and by its irregular growth. The tumor occurs as a hard, firm mass, varying in appearance according to its location. In the breast, which is its usual site, it forms a hard, rounded or irregular mass, which soon becomes firmly attached to the subcutaneous tissue, and eventually to the skin. By the contraction of the fibrous stroma it causes retraction of the nipple and puckering or dimpling of the skin—"bacon-rind" skin. (See Fig. 204.)

On section, it presents a grayish-white glistening appearance, dotted with yellow patches of fatty tissue. The fibrous bands and fatty areas are more marked toward the center of the tumor. Toward the periphery it is more vascular and less fibrous; it is nonencapsulated. On microscopic section, the tissue is composed of two structures, connective tissue and epithelial cells, the connective tissue or stroma being arranged so as to form a series of rounded or irregular spaces (alveoli) in which the epithelial cells are nested. The blood-vessel walls are thickened and fibrous. Microscopic section from the central part of the tumor will show the connective tissue more dense and fibrous and the

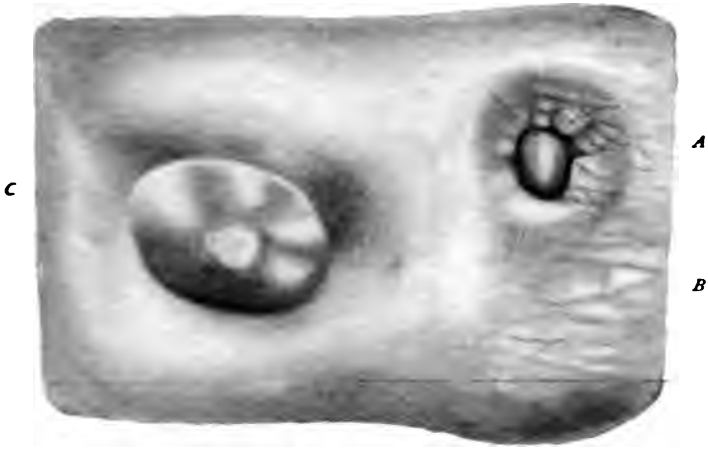

FIG. 204.—PART OF CUTANEOUS SURFACE OF RIGHT MAMMA, THE SEAT OF A CENTRALLY PLACED, PRIMARY SCIRRHOUS CARCINOMA AND OF A SECONDARY NODULE.

Just to the left of the letter *A* is the nipple, showing the retraction or umbilication, with puckering or dimpling of the skin of the surrounding areola. The "bacon-rind" appearance is even more marked just to the left of *B*. To the right of *C* is a secondary nodule, firmly attached to the skin, which is drawn in around the neoplasm; the surface of the nodule shows the stretched skin, which at the five pale ovoid or irregular areas is greatly thinned.

alveoli much smaller, with the epithelial cells small and atrophied, or possibly degenerated. With the increase in the fibrous stroma there is increased contraction, causing irregularities of the surface; when occurring in the breast, this contraction gives rise to retraction of the nipple—umbilication.

During the development of the morbid process contraction of the fibrous tissue may be more rapid than epithelial proliferation, and the organ involved—for example, the breast—may actually diminish in size with progressive induration; when this contraction is marked, the tumor is said to be atrophic or "withering."

(See Atrophic Scirrhus.) Another diagnostic point depending upon the contraction of the fibrous tissue is the "cupping" of the center of the mass when divided by an equatorial incision; this is not always present, but can usually be demonstrated. If the neoplasm be cut in halves by a clean, smooth incision, the central part of the cut surface of each half will retract, thereby

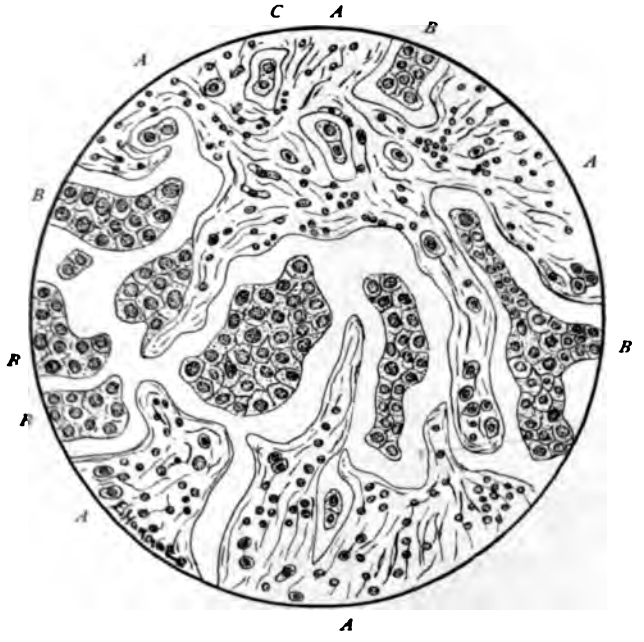

FIG. 205.—GLANDULAR CARCINOMA OF THE LIVER (SCIRRHUS).

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. Drawn from ⅙-inch obj., ½-inch oc. *A, A, A, A, A.* Connective-tissue stroma. *B, B, B, B, B.* Epithelial cells occupying, but not filling, the alveoli. Communication between the alveoli is well shown, as practically all the large alveoli communicate. Just below *C* is shown a small alveolus containing two epithelial cells, and a little to the right is a similar alveolus. A number of efforts were made to demonstrate that the clear space surrounding the epithelial cells was occupied by some material that would not stain by the method used in the section from which this drawing was made. All efforts to secure such demonstration were futile. It is probable that the space is produced by the contraction of the epithelial cells during the process of fixation or hardening, or that the spaces shown are filled during life with some fluid not coagulable by the fixing method used.

depressing that part of the incised surface below the surrounding margin—the depressed area constituting the so-called "cup."

Glandular involvement usually takes place within the first year.

Degenerative Changes.—The forms of degeneration that are likely to occur are fatty, colloid, mucoid, and hyaline, and,

rarely, caseous necrosis. Melanotic, or pigmentary, and calcareous infiltrations occur.

Site.—Most common in breast, uterus, stomach (pylorus), esophagus, rectum, and kidney; rare in ovary, testes, and prostate.

Atrophic Scirrhus.—When the production of fibrous tissue predominates, and the epithelium proliferates but slowly, the resulting tumor contracts much more rapidly than it grows. The epithelial cells are therefore pressed upon, and often disappear from many areas. This form of scirrhus is a breast tumor, and, once developed, it is generally found that the gland and tumor progressively diminish in size. The malignancy is low, and if the fibrous tissue development persists in its excess, the patient rarely succumbs. The writer had a case under observation, a woman seventy-two years of age, who had refused an operation nearly twenty years previously. The entire breast of one side, and the overlying and adjacent skin, showed puckering and contraction; the breast of the other side was also invaded, but ulceration had not taken place over either gland.

Glandular involvement may be long delayed, or, in a few cases, may not occur. In the case just mentioned there was very slight involvement in the last few years only. The patient died at seventy-four, of erysipelas.

Microscopically, such tumors are mostly fibrous stroma, with few alveoli; the contained epithelial cells are advancedly atrophied or degenerated, or both.

2. Encephaloid Carcinoma (*Medullary Carcinoma, Soft Cancer, Acute Cancer*).—This rare variety of carcinoma is a soft, rapidly growing, brain-like tumor, in which the fibrous stroma is more nearly embryonic, not uncommonly myxomatous, and very scanty; the alveoli are large, and are filled with large, rapidly growing epithelial cells. The tumor appears as a soft, at times almost fluctuating, nodular mass, which tends to ulcerate and to bleed (fungus hæmatoides). There is early involvement of the skin ("bacon rind"), soon followed by superficial necrosis and ulceration. As a rule, encephaloid carcinoma occurs earlier in life than scirrhus, and has been reported in the young. It may occur as a primary or secondary growth. The growth is exceedingly rapid, and glandular involvement takes place early—within the first six months. There is no retraction of the nipple when occurring in the breast, and the rapidity of growth produces a more clearly circumscribed mass than scirrhus; it is, however, more rapidly fatal.

Site.—Primarily, most common in mammary gland and in

testes; may occur as a secondary growth following scirrhus, particularly when the latter involves the internal organs. Encephaloid cancer is much less common than scirrhus.

Colloid or **gelatiniform carcinoma** is a form of cancer in which degenerative changes take place in the protoplasm of the epithelial cells of the alveoli or in the connective-tissue stroma. The typical colloid cancer belongs to the glandular group, although a similar change is sometimes observed in the cylindric-cell epithelioma, particularly of the liver. The two conditions are, however, by no means identical, and are therefore easily differentiated. Gelatinous transformation of glandular carcinomata occurs frequently in cancer of the intestinal canal, particularly of the stomach, and less frequently in cancers of the mammary gland, testes, and ovaries. Gelatinous areas are sometimes

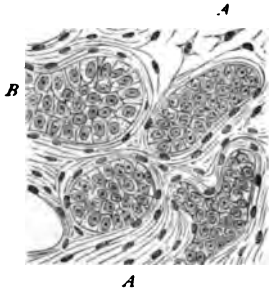

FIG. 206.—ENCEPHALOID CARCINOMA (SOFT CANCER).—(*Gould.*)

A, *A*. Stroma made up of developing connective tissue. At the upper *A* the stroma is almost myxomatous. *B*. Epithelial cells occupying an alveolus; three other alveoli are shown.

FIG. 207.—GLANDULAR CARCINOMA IN WHICH THE STROMA HAS BEEN CONVERTED INTO MUCOID TISSUE.—(*Gould.*)

Note the stellate cells, so closely resembling those seen in myxoma.

found that no longer contain any of the structural elements by which we identify carcinomatous processes. In the younger parts of the tumor, however, advancing transformation may usually be recognized; a varying number of epithelial cells may be found, centrally placed in the alveolus, and surrounded by concentric lamellæ of gelatinous material. The tumors are soft and trembling, glassy, and at points semitransparent. In the mammary gland metastasis may be delayed; in the stomach rapid extension to the peritoneal surface, and more or less diffuse carcinomatosis of the serous surface, may be rapidly developed. (For the chemistry of colloid and mucoid changes see p. 245.)

Mucoid Carcinoma.—When the substance that distends the alveoli is more viscid in character, it is believed to be a mucoid

degeneration of the intercellular substance, rather than a colloid change commencing in the cell. It is the transformation of the albuminoid constituents of the tissue into *mucin.* Until our methods of differentiation become more accurate, and until we know more of the evolution of mucoid and colloid carcinomata, it would probably be best to consider them both under the head of *gelatinous* or *gelatiniform cancer.*

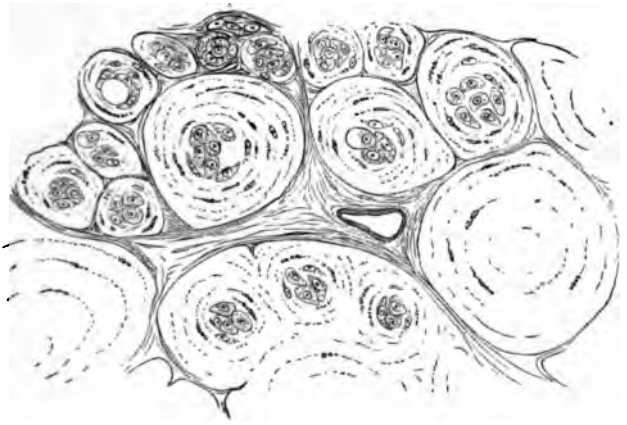

FIG. 208.—COLLOID CANCER.—(*Rindfleisch.*) × 300 diameters.
The stroma has been but little involved, while the intra-alveolar structure has been converted almost entirely into gelatiniform material.

Melanotic carcinoma is, in the writer's experience, a very rare tumor. It is believed that the pigment-forming cells of epithelial origin are present in certain forms of cancer, and that melanosis in such tumors is due to the activity of these cells. Melanotic cancers are usually malignant to a high degree, manifesting a tendency to metastasis early; the secondary nodules are pigmented.

CONNECTIVE-TISSUE TUMORS.

ADULT CONNECTIVE-TISSUE TUMORS.

I. Lipoma.—*Varieties.*—(*1*) *Simple;* (*2*) *fibrous.*

A lipoma or fatty tumor is a localized, more or less circumscribed, new formation of fat. Lipomata are usually lobulated, soft, doughy, pseudofluctuating, and inelastic. As to shape, they are ovoid, spheric, or flat, commonly sessile, rarely pedunculated. If encapsulated, the capsule is exceedingly thin; nonencapsulated fatty tumors are sometimes spoken of as *diffuse lipomata*, the margins being often not clearly defined. Lipomata are rarely

multiple; instances, however, occur in which a large number may be present. The author recalls a case in which the presence of lipomata of the axilla, groin, and neck led to the diagnosis of Hodgkin's disease. The diagnosis in this case was made more difficult by the presence of calcareous infiltration and true bone formation in the interior of the tumors, rendering them more dense and causing a striking resemblance to multiple lymphadenomata. Multiple lipomata are said to occur in families; not infrequently the inherited tendency is transmitted through several generations. An interesting phenomenon observed in fatty tumors

FIG. 209. FIG. 210.

DIFFUSE LIPOMA OF THE NECK.

Case reported by Dr. J. Shelton Horsley in the "Philadelphia Medical Journal," July 8, 1899 (reproduced by permission).

is "gravity wandering"; this feature may be present in tumors developing in the subcutaneous tissues and possessing slight attachment to the surrounding structures. Fatty tumors developing on the upper portion of the chest-wall, near the axilla, or on the back, may, in the course of time, descend to the level of the pelvic brim, and lipomata of the thigh may wander as far as the knee. The distance traveled and the rapidity of movement are, of course, influenced by the amount of attachment and by anatomic relations.

Microscopically, fatty tumors consist of cells containing fat and of a variable quantity of connective-tissue stroma. The cells are like those of adipose tissue, though usually larger. The blood-vessels are distributed in the fibrous stroma. If the fibrous tissue is in excess, the neoplasm is called a **fibrolipoma**, or fibro-fatty tumor. The fibrous fatty tumor, or fibrolipoma, differs from the **simple lipoma** only in the amount of fibrous tissue that it contains. In the fibrolipoma this is abundant; there is no capsule, and, if the tumor be grasped at its base and the skin made tense, dimpling of the cutaneous covering occurs, owing to the fibrous bands that traverse the tumor pulling the skin in at their points of attachment. Lipomata containing myxomatous tissue are called *myxolipomata*.

Fig. 111.—Lipoma. × 125. The cells are like those of adipose tissue, though usually larger. The blood-vessels are well shown.

Clinically, lipomata are benign tumors of slow growth and of variable size.

The *infiltrations and degenerations* that they may undergo are calcareous infiltration and mucoid degeneration, ossification, ulceration, and cystic degeneration; secondary inflammatory and necrotic changes also occur.

Site.—Connective tissue; subcutaneous tissue of trunk, especially of back and abdominal walls; intermuscular septa; subsynovial and subserous tissues; rare in stomach and intestines and in internal organs.

II. Chondroma (*Enchondroma, Enchondrosis, Chondroid Exostosis*).—Chondromata are masses of new tissue, composed of hyaline, elastic, or white fibrocartilage. Chondromata developing from preexisting cartilage, such as the cartilages of the larynx and trachea and the costal cartilages, may assume a polypoid shape, and are not uncommonly multiple, and are spoken of as *ecchondromata*. Developing from bone or in tissue not normally containing this element, the cartilaginous tumors are called *enchondromata*. The term *chondroid exostosis* is applied to a cartilaginous tumor growing from bone; such a tumor may appear as a periosteal, subperiosteal, or medullary growth. Cartilaginous tumors are usually rounded, smooth, tuberous, or lobulated tumors of very dense consistence; they often appear to be encapsulated, owing to the compression of the surrounding tissues; not uncommonly, however, they have a well-marked capsule. The cut surface presents a pearly, bluish-pink appearance, identical with fresh cartilage. As a rule, cartilaginous

tumors are nonvascular; but if vascularization occurs, it is at the center or through the fibrous septa. Tumors composed of cartilage are most frequent in the young, and are rare after puberty.

Microscopically, they resemble true cartilage tissue; the intercellular substance may be hyaline, faintly or distinctly fibrous, or, in rare instances, mucoid. They are not, as a rule, composed of dense cartilaginous tissue, but of islands of cartilage surrounded by fibrous septa. The cartilage matrix is hyaline, except at its junction with the fibrous stroma, where it is usually more or less fibrous. Within the matrix are the lacunæ containing the cartilage cells; these resemble the normal cartilage, and are either rounded or oval in shape. The lacunæ of the matrix are occasionally branched, so as to cause the appearance of a series of stellate spaces, with cartilage cells lying in their centers.

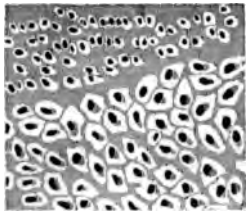

FIG. 212.—CHONDROMA.—(*Gould.*)

Infiltrations and Degenerations.—Fatty, calcareous, mucoid (most common), and cystic; ossification may occur, especially when the tumor springs from the junction of the epiphysis and shaft of a long bone.

Site.—Bones; as bones are developed largely out of cartilage, it may be supposed that remnants of the embryonic cartilage are left over, and that they afterward develop into tumors. Chondromata occur most frequently on the metacarpal bones and phalanges of the hands; not so frequently on the corresponding bones of the foot. They are not infrequent on the femur and bones of the pelvis, in the last-named situation not uncommonly attaining the largest size; they also occur on the ribs and scapulæ, rarely on the face and skull, sheaths of tendons, and bronchial cartilages. Chondromata are infrequent in the soft parts, but have been observed in the testicles, ovaries, mammæ, and salivary glands. Chondroid and osteoid masses occasionally develop from the inner table of the skull and from points of junction of the cranial bones that normally coalesce.

III. Osteoma.—A tumor-like mass of bone developed without the occurrence of inflammation or incident to the process of repair; usually occurring at the point of junction between a bone and its cartilage. Osteomata are classified, according to their position, as (1) **exostoses,** or those growing from the exterior of a bone, and (2) **enostoses,** or those growing from the interior of a bone. According to their structure they are divided into (*1*) *eburnated;* (*2*) *compact;* (*3*) *cancellous* or ***spongy.***

1. Eburnated Osteoma.—These occur most frequently on the inner table of the skull, and are not uncommonly syphilitic. They are extremely hard, symmetric, and usually multiple. On section, the dense bony structure is found to be composed of lamellæ, which are arranged parallel with the surface of the tumor. In the lamellæ there are no blood-vessels and no Haversian canals, but canaliculi similar to those found in the cementum of the teeth; these run toward the surface.

2. Compact Osteoma.—This variety is composed of ordinary compact bone, similar to that found in the outer layer of the long bones. The growth is nodular, usually beneath or in the periosteum, and is commonly met with in the long bones. On section, it is found to differ from the eburnated osteoma, in that the vessels and Haversian canals run at right angles to the long axis of the bone. The tumor possesses a periosteal fibrous covering, with a layer of small round cells (osteoblasts), and with young bone formation in progress beneath. Regular Haversian systems may be clearly defined.

3. Cancellous or Spongy Osteoma.—In this variety the trabeculæ are very thin and are not numerous; the medulla is embryonic in character, and often appears as a gelatinous mass. In rare cases it is distinctly fibroid. The whole tumor is essentially like the spongy tissue of which the ends of long bones and the bodies of shorter ones are composed.

Clinical Characteristics.—Osteomata are benign tumors of slow growth, usually arrested with advancing age, and rarely attaining a large size. They are often hereditary and multiple, in which case they usually occur in early life. Osseous growths that exhibit malignant characteristics are *osteosarcomata*, or *sarcomata* that have undergone partial ossification or extensive calcareous infiltration.

Secondary Changes.—Osteoma may become inflamed, may become carious, or may undergo *necrosis*. Rarely an osteoma may be transformed into a sarcoma.

Site.—Most common in connection with bone, periosteum, medulla, or cartilage; may occur in the soft parts of the body, in the brain substance, in the dura mater and pia mater, in the pleura, diaphragm, and pericardium, in the skin, in the choroid coat of the eye, in the air-passages, around or in glands, in nerve-centers, and in tendons.

IV. Fibroma (*Fibroid, Desmoid, Steatoma, Inoma*).—Fibromata are tumors composed of wavy bundles of fibrous tissue.

Simple Fibroma.—This variety is typified by the *painful subcutaneous tubercle*, which consists of a tubercle about the size of a

coffee-bean in the subcutaneous cellular substance. It is of firm consistence, and is apparently quite circumscribed, being situated loosely in the cellular tissue immediately under the integument. From the extreme pain produced by these small nodules, many have imagined that they must contain nerve-fibers; careful research, however, has in all cases failed to demonstrate their existence. They occur more frequently in the female than in the male.

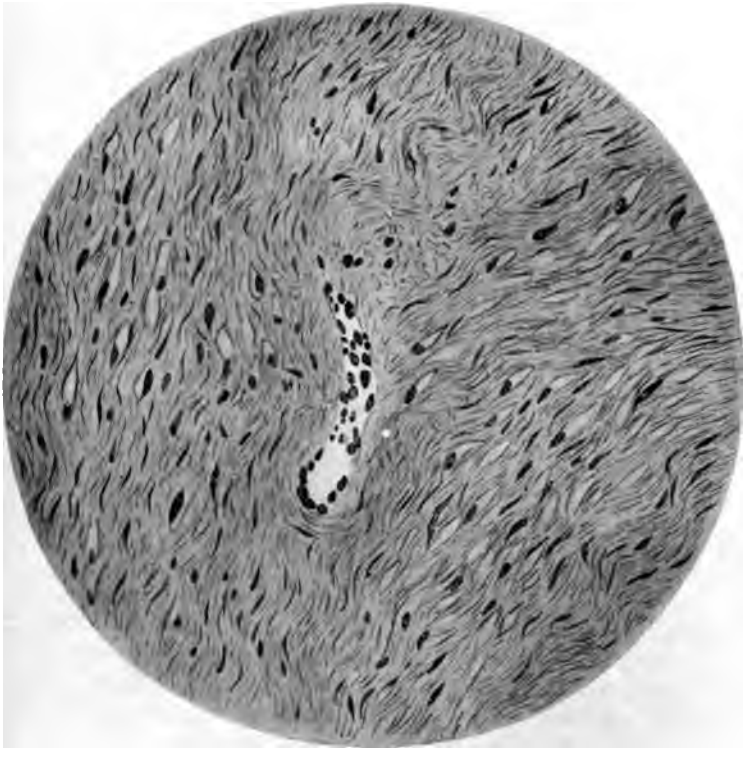

FIG. 213.—SOFT FIBROMA.

By some authorities fibromata are said to be *hard* or *soft*, the density being dependent upon the degree of development. The hard or dense fibroma (*fibroma durum*) is of the type of dense fibrous tissue, while the soft fibroma (*fibroma molle*) is composed of a younger cell growth, and contains fewer fibers and more cellular elements. The hard fibroma is firm, usually lobulated, and encapsulated. The soft fibroma is much less dense, and in tex-

ture resembles the lipoma; it may be lobulated and encapsulated. The density of the fibroma, upon which the foregoing subdivision is based, may be dependent upon factors other than the developmental stage of the fibrous element. Myxomatous transformation of the intracellular substance (*myxofibroma*) and edema produce soft, often semifluctuating fibrous masses. In addition to the fibrous tissue, other connective-tissue elements may be present; when such elements are sufficiently abundant, the condition is indicated in the following manner: For fatty tissue, *lipomatous fibroma*, or *fibroma lipomatodes;* for bony tissue, *ossifying fibroma*, or *fibroma ossificum;* a fibroma rich in capillaries is called *angiofibroma* or *telangiectatic fibroma*, or *fibroma telangiectaticum.*

Molluscum Fibrosum (Synonyms: *Fibrocellular Tumor, Dermatolysis, Pachydermatocele*).—This variety of fibroma occurs in a rather extraordinary condition, in which the chief feature is an overgrowth, apparently not inflammatory, of the fibrous structure of the skin and subcutaneous tissues. The new growth may affect a small area, such as the scalp, or it may involve a large extent of skin on the trunk or extremities, or both, causing it to hang in pendulous folds. Sometimes the tumors form as separate nodules scattered over the skin. Microscopically, the tissue is composed of fibrous bundles with intervening branched cells, the processes of which clasp the bundles. In the dense fibrous bands there are few cells. The cells are, in many instances, almost embryonic in appearance, and the tissue is particularly rich in nuclei.

Merken has recently studied fibroma molluscum, and concludes that it depends upon some congenital factor closely allied to that operative in the production of nevus.

Keloid (*Cheloid, Kelis*).—This is a rare variety of fibroma. It takes the form of tuberous, sausage-like, or discoid growths seated in the corium beneath the papillary layer.

Varieties.—(*1*) *True* or *spontaneous keloid;* (*2*) *cicatricial keloid.*

1. **True Keloid.**—This consists of a fibrous growth in the corium, covered with a papillary layer; the papillæ and epidermis are intact. It is most common in the negro. It consists of bundles of coarse fibers, and in the early stage contains numerous spindle cells.

2. **Cicatricial Keloid.**—This variety grows in the substance of a scar, and differs from the true keloid in that it is not covered by the papillary layer. In other respects it resembles the true keloid.

Site.—Fibromata originate in connective tissue, cutis, or subcutaneous tissue, from submucous or subserous tissue, from fascia, periosteum, neurilemma, or the connective tissue of organs (uterus,

ovaries, testicles, mammary gland, and labium majus). Clinically, they are benign tumors of slow growth, and, with the exception of keloid, do not tend to recur after removal.

Degeneration.—Serous infiltration (as in molluscum fibrosum), mucoid degeneration, fatty degeneration (especially in the simple fibroma of syphilitic origin), calcification (*fibroma petrificum*); suppuration and ulceration also occur.

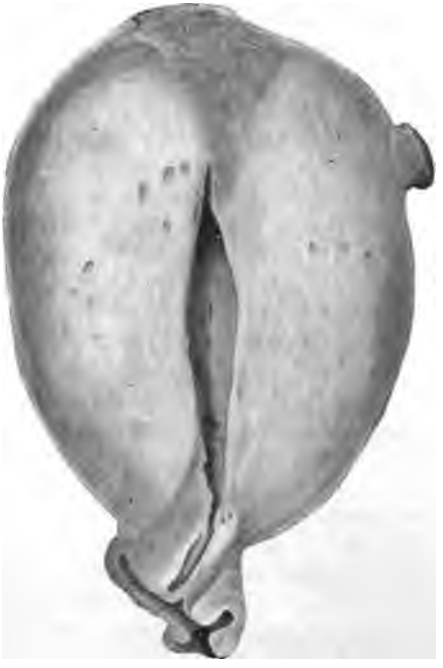

FIG. 214.—SECTION (LONGITUDINAL) OF THE UTERUS SHOWING UNIFORM MYOMATOUS ENLARGEMENT.

At *A* is a small subserous myoma beginning to form a pedicle. The small depressions shown on the incised surfaces are sections of sinuses, some of which contained thrombi.—(*From a specimen in the museum of the Jefferson Medical College.* The drawing is one-fourth natural size; the artist has slightly exaggerated the transverse diameter of the uterine cavity. Weight of specimen, 5760 gm.)

V. Myoma.—The myomata are tumors composed of muscle-tissue. Two forms of the myoma are recognized, depending upon the kind of muscle that the tumor attempts to simulate. A tumor composed of nonstriated muscle-fiber is called a *leiomyoma*, or *myoma lævicellulare*; a tumor containing a varying amount of striped muscle-fiber has been described, and is called *rhabdomyoma*, or *myoma striocellulare*.

1. Liomyoma.—These tumors occur most frequently in the uterus, and not uncommonly contain more fibrous tissue than similar tumors occurring elsewhere. Liomyomata also occur in the prostate, esophagus, stomach, and intestines. As a rule, this variety of tumor arises only in situations containing unstriped muscle-fiber. The tumors vary in size. Myomata of the intestinal wall are usually small; myomata of the uterus may attain the size of a fetal head, or, in rare instances, they may be larger; a number of instances have been reported in which the tumor weighed over one hundred pounds. Severanu removed a uterine myoma weighing 195 pounds.* Myomata may be *single or multiple*. Multiple myomata, as when a number of tumors occupy the same organ, give rise to a tuberous, bossed, lobulated, or irregular surface. Myomata in the intestinal wall may project from the serous surface as distinct, pedunculated tumors. The same condition is possible in the uterus. *Uterine myomata* are said to be *subserous* when situated immediately beneath the peritoneum, *submucous* when located immediately under the mucous membrane, *interstitial*, or *intramural*, when more or less centrally placed in the uterine wall. Most authorities agree that all uterine myomata begin as interstitial, or intramural, growths. As a result of the contractile power of the normal uterine muscle, as well as of the pressure brought to bear upon the tumor by its continuous enlargement, it is forced along the line of least resistance, which must be toward the serous or mucous covering. A submucous myoma may become a *pedunculated polyp*, the length of the pedicle varying in different cases. Sometimes the pedicle may be sufficiently long for the polyp to project from the os uteri, or even from the vulvar orifice. Similarly formed subserous polypi occur. As a result of twisting or kinking of the pedicle the blood supply to the polyp proper may be arrested, and extensive necrosis, or even gangrene, may occur.

FIG. 215.—LIOMYOMA.—(*Gould.*)
The rod-shaped nuclei are shown in longitudinal section of the pseudobundles at the margin, and in transverse section in the center, of the illustration.

Wherever a myoma occurs it may be distinctly circumscribed, surrounded by fibrous capsule, or an ill-defined irregular mass in the midst of the muscle-tissue.

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* Williams, "Lancet," Sept. 23, 1899.

Microscopically, liomyomata are made up of elongated spindle-cells, with rod-shaped nuclei, more or less distinctly grouped into fasciculi of various sizes; the connective tissue varies in quantity. The irregularly arranged muscle elements pass in all directions through the tumor. The few blood-vessels present are found in the connective tissue. Occasionally, liomyomata are telangiectatic. Such richness in blood-vessels, however, is rare. More frequently a tumor contains comparatively large, irregular sinuses, which, in the larger tumors, may attain a transverse diameter of from 1 to 1.5 cm., and possess a tortuous length of from 5 to 10 cm. Such irregularly formed cavities may contain thrombi. (See p. 272.)

Secondary Changes.—Of these, the most frequent are calcareous infiltration (so-called "womb-stone") and fatty and myxomatous degenerations. Inflammation (due to injury), abscess formation, ulceration, and other necrotic processes occur. Clinically, the liomyomata are benign tumors, but sarcomatous transformation is occasionally seen.

2. Rhabdomyoma.—This variety of myoma, made up of, or containing, striped muscle-fiber, is exceedingly rare, and is usually congenital. It is not improbable that tumors of this class are met with only as a result of the higher evolution of sarcomatous tissue (*myosarcoma*), in which the imperfectly developed muscle remains, for the most part, in an embryonic stage.

The muscle-fibers present in rhabdomyoma are irregularly formed, and are often more or less spindle-shaped or club-shaped. As already stated, the tumor is in most instances congenital, and is usually found in the kidney, heart, or uterus.

VI. Angiomata are tumors formed of, or following, the type of vessels—either blood-vessels or lymph-vessels. The term angioma has been applied to tumors composed of blood-vessels, and has that significance when used alone. For the purpose of description it is purposed to divide the angiomata into hemangioma and lymphangioma.

(A) **Hemangiomata** are tumors consisting of blood-vessels bound together by a small amount of connective tissue. Some of these may be composed of newly formed blood-vessels, while others consist of more or less altered preexisting vessels. The pure hemangiomata are composed of tissue entirely of new formation, but, by many, the tumors formed by alteration in preexisting vessels are included under this name.

Varieties.—(*1*) *Simple*; (*2*) *cavernous*; (*3*) ***plexiform.***

1. Simple Hemangioma (*Simple Nevus, Telangiectoma, Birthmark, Mother's Mark, Angioma Telangiectoides*).—This is the most

common variety, and affects the skin and subcutaneous tissues. Simple hemangiomata are flat, slightly elevated, sessile tumors of a violet or dark-red color, rarely bright red or pink; they are most frequently located upon the face, around the orbit, or on the neck, are usually congenital, and after birth may increase in size. On section, the vessels are found to be thin-walled (dilated, fusiform, cylindric, sacculated, or spheric), and to be embedded in a fibrous or cellulo-adipose matrix. There are usually two or more large vessels that establish a communication between the nevus and an adjacent artery or vein.

Site.—Skin of the face, scalp, neck, and back. May occur on the labia, lips, tongue, and conjunctiva; rarely on the limbs. The varieties of simple hemangioma are: (*1*) *Nevus flammeus* (strawberry mark). These marks are of a bright-red color. (*2*) *Nevus vinosus.* These are of a dark-red or port-wine color, and are known as *port-wine marks.*

2. Cavernous Hemangioma.—This variety differs from simple hemangioma in that the vessels are less tubular. The tumor is composed of a series of irregular cavities formed by thin, fibrous septa. On section, these cavities appear as irregular sinuses separated by a nucleated fibrous network of spindle-cell tissue. Many of the walls are incomplete, which fact shows the communication of the spaces. The cavity walls are lined with endothelium. Cavernous hemangiomata are spoken of as *erectile tumors,* owing to their resemblance to the erectile tissues, such as the corpus cavernosum of the penis. They are rarely congenital, and may develop from preexisting simple hemangioma. Usually they occur early in life, and are rare in old age. When this form of tumor occurs in the skin and forms a livid, raised, and uneven patch, it is referred to as a *nevus prominens.*

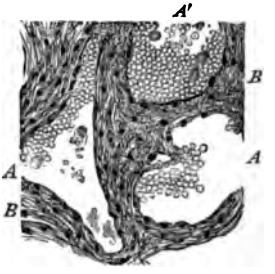


FIG. 216.—CAVERNOUS HEMANGIOMA.—(*Gould.*)
A, A. Caverns that were filled with blood during life, as is the upper one at *A'*. *B, B.* The fibrous walls of the caverns.

Site.—Common in the skin and subcutaneous tissue, and occasionally in the liver; may occur in the kidney, spleen, uterus, intestines, bladder, voluntary muscle, bone, mamma, tongue, larynx, subperitoneal tissue—in fact, in almost any vascular tissue.

3. Plexiform Hemangioma (*Racemose Aneurysm, Aneurysm by Anastomosis, Cirsoid Aneurysm*).—Properly, this is not a neoplasm, but a pathologic alteration of the vessel. The vessels

become dilated and convoluted; the dilated vessels press on the intervening tissue and cause atrophy. The vessel-walls are usually thickened. The tumor may be congenital or acquired. When occurring in the most superficial vessels, it is by some called a *nevus vasculosus*. Plexiform angioma has been observed to follow injury.

Site.—Scalp (frontal and temporal region), extremities, labia pudendi, and spermatic cord.

(B) **Lymphangioma** is a tumor made up of dilated lymph-vessels. Rarely, the dilated vessels may form distinct caverns or sacs—the *cavernous lymphangioma*. More commonly, the masses are of dilated vessels, and hence are analogous to the telangiectatic hemangioma already described. The tracts are the lymph-vessels, and not blood-vessels.

Site.—Lymphangioma occurs most frequently in the tongue or lip, constituting *macroglossia* and *macrocheilia* respectively. In both these localities it is not uncommonly associated with what appears to be a proliferative change in the unstriped muscle present. A special form of lymphangioma occurs in the lymphatics carrying chyle (chylous vessels, lacteals), and is called a *chylangioma*.

VII. Lymphoma, or tumor of the lymph-gland, covers a multitude of conditions, many of which are in no sense tumors. Thus, the glandular enlargements of tubercle, syphilis, etc., are known as tubercular or syphilitic lymphomata. To the same group belong the inflammatory lymphomata that accompany many infections: *e. g.*, chancroidal lymphoma, suppurative lymphomata of various kinds, and the glandular enlargements found in the cervical glands in various throat affections, such as diphtheria and scarlet fever, not any of which are tumors.

Lymphosarcoma is a sarcoma of the lymph-gland, and differs but little from other forms of sarcoma except in such histologic peculiarity as must arise from the site. The lymphatic enlargement that accompanies leukemia is probably an infectious process, with hypertrophy and hyperplasia of the cells and stroma of the lymph-gland, or is a form of sarcoma attacking the lymph-glands: the latter view may be considered as most popular at present. Such a condition is noted in Hodgkin's disease, when the hypertrophied glands are known as lymphadenomata. (See Diseases of the Lymph-glands, part III.)

VIII. Myxoma.—This form of tumor is composed of mucous tissue, which is not, strictly speaking, an adult structure; it is, at least, the lowest grade of adult connective tissue. The tissue is identical with that surrounding the vessels of the

umbilical cord (Wharton's jelly), and resembles the vitreous humor. The tumor always contains a certain amount of fibrous stroma, and resembles an edematous fibroma. In fetal life myxomatous tumors are met with in those subcutaneous tissues from which fatty tissue is later developed. Macroscopically, the tissue appears as a homogeneous, structureless, gelatinous mass. The majority of the cells present are angular and stellate, with long anastomosing prolongations; others are indistinct (owing to the refractory nature of the intercellular substance), oval, spheric, or fusiform in shape. The blood-vessels are readily located, but are few in number. Frequently, between the cells fine elastic fibers can be demonstrated.

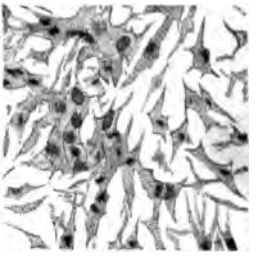


FIG. 217.—MYXOMA.

Clinically, myxoma is a peculiar, soft, gelatinous tumor, grayish or reddish-white in color, and on section yields a gelatinoid, whitish, albuminous, or mucilaginous material. Myxomata usually occur after middle life, are of moderately slow growth, may be single or multiple (commonly multiple), vary in size (rarely large), and not uncommonly recur after removal. This return may not be a true recurrence, but may be due to imperfect removal, after which the remaining myxomatous elements develop. Myxomata may be pedunculated or sessile; rarely, the mass is lobulated. Primarily, they are benign tumors.

Secondary Changes.—Hemorrhage (capillary), if extensive, may form blood cyst; fatty degeneration; they may become inflamed, ulcerated, or necrotic.

Site.—Connective tissue; most common in subcutaneous and subserous fat; submucous (nares, uterus) and intermuscular tissues; rare from periosteum and medulla of bone, connective tissue of organs, and perineurium. Myxomata occasionally spring from the placenta (one form of *uterine hydatids*, probably incorrectly so called).

EMBRYONIC CONNECTIVE-TISSUE TUMORS.

Sarcoma.

Varieties:

1. *Round-cell* (small and large).
2. *Spindle-cell* (small and large).
3. *Giant-cell* (myeloid).
4. *Mixed-cell.*
5. *Alveolar.*

The sarcomata are tumors composed of embryonic connective tissue in which the cellular constituents predominate over the intercellular substance. The embryonic cells tend to infiltrate the surrounding tissues, as a result of which sarcomata are rarely, if ever, encapsulated. If a capsule surrounds the growth, it may result from condensation of adjacent tissues, or it may be a part of the tumor; in either case it is sure to be infiltrated by the tumor cells.

Histology.—All sarcomata consist of embryonic connective-tissue cells embedded in a peculiar intercellular substance, which intercellular substance varies in amount and character. As a rule, the sarcomata contain very little true fibrous tissue, the whole mass being composed of embryonic cells; the cells are uninucleated or multinucleated, and rarely possess a limiting membrane; the shape, size, and arrangement of the cells determine the variety of the tumor. The intercellular substance, which is usually small in amount, is closely connected with the cells, as in all connective tissues. The consistence of the tumor depends upon the character of the cell and intercellular substance, and upon the presence or absence of a fibrous stroma. The blood-vessels are very numerous, and are usually in direct contact with the cells, or they may be separated from them by a layer of thin fibrillated tissue. The vessels frequently lack distinct walls, the wall being composed of densely packed embryonic cells. These cells may become detached, and may be carried along in the current; hence, *sarcoma spreads by the blood-vessels.* Owing to the thinness of its walls, hemorrhage, with extravasation of the blood, takes place; when this occurs, the tissue becomes pigmented, and the tumor is known as *melanotic;* or this extravasated blood may become encysted (blood cyst). As will be seen later, melanosis may arise from other causes. As a rule, the edge of the tumor is not clearly defined, there being no line of demarcation between the tumor and adjacent structures. When the tumor is of slow growth, an apparent capsule may be formed of the surrounding connective tissue, due to condensation.

Clinical Characteristics.—As a rule, sarcomata occur most frequently in early and middle life, but may occur at any age, and are among the most malignant of tumors. They are characterized by their tendency to extend locally, to infiltrate surrounding structure, to recur after removal, and to give rise to metastasis. They may be localized, and at first sharply circumscribed; but are liable to become rapidly disseminated, both by local infiltration and metastasis. Secondary growths occur most fre-

quently in the lung. Sarcomata may disseminate much more rapidly than carcinomata.

The round-cell and large spindle-cell variety are of rapid growth and are very malignant. The small spindle-cell variety is much firmer, of slower growth, and less malignant. When occurring in bone, if subperiosteal, they are more malignant than when located in the center of the bone.

The following are the chief signs of malignancy in any tumor, be it sarcoma or carcinoma. They are inserted here by reason of their special applicability to the sarcomata:

1. Size of the Cell.—As a rule, it may be said that the smaller the cells of a tumor, the more malignant will it probably be. Thus, the small round-cell sarcoma is a more malignant tumor than that composed of giant-cells, and the small epithelial cells of a scirrhous cancer of the mamma give rise to a more malignant growth than the large, flat epithelial cells of the skin, as seen in the squamous epithelioma.

2. The Number of the Cells.—If a tumor be purely cellular, the likelihood of its recurrence is great.

3. Activity of the Cells.—One of the chief diagnostic features of a malignant tumor is the tendency of its nuclei and cells to divide; if on section a large number of the cells show mitosis in some stage of progress, the prognosis is unfavorable, recurrence being almost a certainty.

4. Shape of the Cell.—A small, round cell, like a lymph corpuscle, will be more readily transported by a blood-vessel or lymphatic than one that is long and tapering; hence the former will have a greater tendency than the latter to reproduce the tumor in neighboring parts. The round-cell sarcoma forms secondary tumors in neighboring organs, infiltrates blood-vessels, and evinces metastasis with greater readiness than one of the spindle-cell type. The foregoing applies not only to local infiltration, but also to distal metastases. The large, irregular cells of the squamous epithelioma will be less likely to reach distant parts through the blood-vessels or lymph-vessels than the small, round, plastic cells of a sarcoma.

5. The Manner in Which the Cells Are Held Together.—So far as regards the sarcomata, at least, the more loosely the cells are held together, the greater is the tendency of the tumor to recur. This is equivalent to saying that the more fluid the intercellular substance, the more malignant the tumor. Fluidity of the intercellular substance implies that the neoplastic cells are loosely held together; this lack of cohesion between the elements of the tumor permits of the ready dislodgment of one or more cells, or

masses of cells, and hence favors displacement of the tumor elements into the lymphatics and blood-vessels. The fluidity of the intercellular substance may be partly judged by the consistency of the tumor; a soft, almost fluctuating tumor, has but little firmness in the intercellular substance. Such soft, pseudofluctuating tumors are not infrequent among the sarcomata. The author has known of one or more instances in which the surgeon has cut into a sarcoma under the impression that he was dealing with a cyst or a cold abscess. Indeed, the cellular elements of some of the small, round-cell sarcomata are so loosely attached that a needle—for example, an exploring needle—passed into the tumor may not infrequently be moved about from place to place, the operator not being able to detect the presence of any solid constituent within the mass.

6. Absence of Any Tendency to Complete Their Development.—Of all signs of malignancy, this, in the case of sarcoma, is perhaps the most unequivocal. The cells do not complete the formation of connective tissue that normally they were destined to generate. Instead of their energy being occupied in the metabolism necessary to secrete the matrix peculiar to each, it is wholly expended in causing the cell to reproduce itself. At certain stages in the process of repair the proliferated cellular elements may constitute a mass of embryonic tissue which, if we take into consideration only the character of the cells, can not be differentiated from sarcomata possessing similar cellular elements. In the tissue elaborated during reparative processes we nearly always see the cellular elements in one or more parts progressing to their proper histologic end—cicatricial tissue, osseous tissue, etc. In some sarcomata an effort in this direction may be apparent. It is, however, never fully successful.

7. Tendency of the Cells to Spread into Neighboring Interfibrillar Spaces.—In examining a tumor, the tissues round about it should be carefully investigated, with a view to noticing whether the cells of the tumor have invaded adjacent structures. If so, such a tumor is dangerous, and should be excised with a wide margin. A single cell left in the surrounding parts will reproduce the tumor. Cancer of the mamma shows more tendency to penetrate the surrounding stroma of the gland than perhaps any other tumor. It is also one of the most malignant of tumors (Hamilton).

1. **Round-cell Sarcoma** (*Encephaloid* or *Medullary Sarcoma*).—This is a rather infrequent form of sarcoma, and consists of round cells with very little intercellular substance. The cells contain large, easily stained nuclei. Blood-vessels are abun-

dant, and appear as channels or sluiceways passing directly between the cells; there are no lymphatics present. The cells rapidly infiltrate the surrounding tissues; the tumor tends to recur

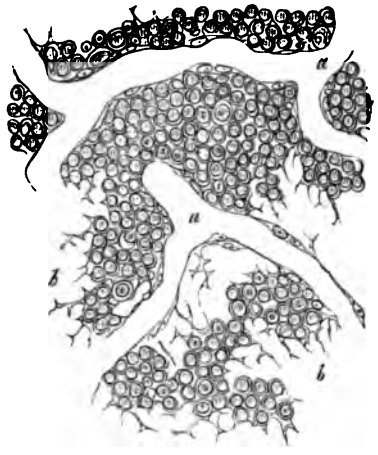


FIG. 218.—ROUND-CELL SARCOMA.—(*Rindfleisch.*) × 300 diameters.
a, *a*. Blood-vessels without distinctly formed walls. *b*, *b*. Points where the round cells have partly fallen out, showing the slight basis of reticular tissue.

after removal, and gives rise to secondary deposits. The variety known as *large round-cell sarcoma* differs from the small round-cell variety in that the cells are larger and more irregular in size; they may be mononuclear or polynuclear. The round-cell sar-

FIG. 219. — ROUND-CELL SARCOMA. — (*Gould.*)

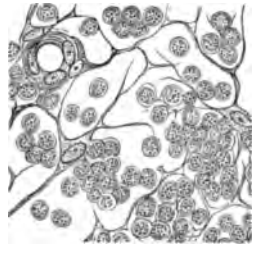


FIG. 220. — ROUND-CELL SARCOMA OF A LYMPHATIC GLAND.—(*Gould.*)
The cells have dropped out at places, showing the remainder of the intercellular trabeculæ.

coma may occur in any tissue and at any age, even in the fetus *in utero*. It is a soft, rapidly growing tumor, which, when on the surface, ulcerates early, and usually proves fatal in a few months.

2. Spindle-cell Sarcoma (*Recurrent fibroid* (Paget); *Fibroplastic Tumor* (Lebert); *Fibrosarcoma; Oat-cell Sarcoma*; (*Fasciculated Sarcoma*).—The spindle-cell sarcomata are the most common. They are firm in texture, and on section are translucent, and grayish or yellowish-white in color. As a rule, the spindle-cell sarcomata are much less malignant than the round-cell variety. They are divided into (*a*) small-cell and (*b*) large-cell.

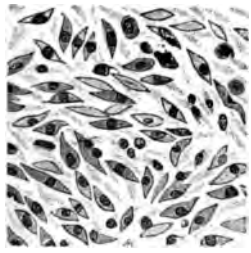


FIG. 221.—SPINDLE-CELL SARCOMA.—(*Gould.*)

(*a*) **Small Spindle-cell Sarcoma.**—This variety resembles somewhat the fibromata; the cells are fusiform in shape, with oval nuclei; the intercellular substance, of which there is very little, may be fibrillated. The bundles of cells pass in every direction. Except that it is firmer, grows with less speed, and does not so quickly ulcerate or prove fatal, the tumor clinically resembles the round-cell sarcoma.

Site.—Most common in the periosteum, fasciæ, eye, antrum, breast, testicle; may occur in any connective tissue. These tumors tend rapidly to infiltrate the surrounding tissue and to recur locally after removal.

(*b*) **Large Spindle-cell Sarcoma.**—This differs from the small spindle-cell variety in that the cells are larger, with prominent nuclei or nucleoli, which are frequently multiple; there is very little intercellular substance, with slight or, it may be, no fibrillation. The tumor is likely to be very soft, and is sometimes stained by extravasated blood; the growth is rapid and the neoplasm very malignant. These tumors frequently become osseous (osteosarcoma or osteoid sarcoma), especially when occurring in the periosteum or bone.

3. Giant-cell Sarcoma (*Myeloid Sarcoma*).—This variety resembles the spindle-cell growths, and usually occurs in connection with bone. Such tumors contain many large polynucleated cells, and often contain fusiform cells like those of the spindle-cell varieties; indeed, giant-cell sarcomata are practically all mixed-cell tumors in which the giant-cells constitute more or less conspicuous elements. In addition to the polymorphism of the cells, such tumors not uncommonly show a certain alveolar arrangement. In properly stained specimens the giant-cells are sometimes sufficiently large to be easily recognized by the unaided eye. In very rare instances the giant-cell sarcomata contain a small quantity of pigment. The large giant-cells are arranged in almost

direct contact with the other cellular elements, there being very little intercellular substance. As a rule, the blood-vessels are not plentiful, but the tumors may become highly vascular and may pulsate; they frequently become cystic. They are usually firm. Giant-cell sarcomata are rare after middle life, and are the least malignant of the sarcomata; they usually spring from the periosteum or endosteum. When they originate in the upper or lower alveolar process, they constitute one variety of the *epulis*.

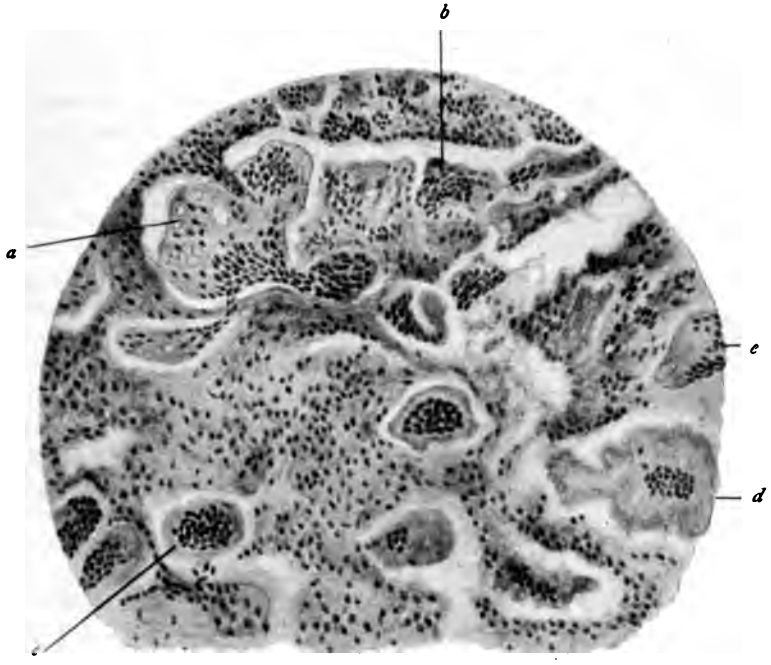


FIG. 222.—GIANT-CELL SARCOMA.—(*Specimen lent the author by Dr. Rosenberger.*)
a, *b*, *c*, *d*, *e*. Giant-cells. The large giant-cell *a* shows vacuolation and dissemination of the nuclei, with pseudopod-like extension suggestive of ameboid movement. This condition is not commonly observed. The cell contains over one hundred nuclei. The giant-cell *c* is more nearly typical. The admixture of other cellular elements—the usual condition noted—is well shown. (⅙-inch objective, 1-inch ocular.)

4. Mixed-cell Sarcoma.—This variety contains round cells (large and small) and spindle cells (large and small), and otherwise resembles the round-cell and spindle-cell varieties. A sarcoma in which all the cells have practically the same size and shape is rarely seen; even when the cells of one area in the tumor are approximately all alike, examination of other areas will usually show cellular elements that are quite dissimilar. To this extent

it may be said that nearly all sarcomata are mixed-cell tumors. As the malignancy, consistency, and, to a certain extent, the other characteristics of a sarcoma depend upon the size and shape of the cells, it will at once become apparent that a tumor largely composed of a certain cell will be most likely to possess the characteristics with which that particular cell is commonly associated. For this reason it is customary to speak of a sarcoma as spindle-cell sarcoma, even though it contains a minimum of cells possessing other shapes. The exception to this rule is in giant-cell sarcoma, where the giant-cells are not abundant as compared with the other cellular elements.

5. Alveolar Sarcoma.—In this the fibrous stroma resembles that of cancer. The nests of cells are separated by thin fibrous bands. The cells are sharply distinguished from the fibrous network, and are loosely adherent. The blood-vessels follow the course of the fibrous tissue and rarely, if ever, enter the cell groups. In handling the sections, should the nests of cells drop out, the remaining fibrous stroma resembles closely transverse sections of air vesicles (alveoli). Under the microscope there is no variety of sarcoma so likely to be mistaken for carcinoma as the alveolar sarcoma. A little experience will usually overcome this danger, particularly if the blood-vessels in the stroma be carefully studied. In the sarcoma many of the vessels are without walls; in the carcinomatous stroma the walls of the vessels will, in most cases, be normal, or may even be thicker than usual. Alveolar sarcomata are not uncommonly melanotic. (See Fig. 225.)

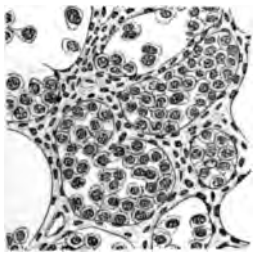


FIG. 223. — ALVEOLAR SARCOMA.—(*Gould.*) Compare with glandular carcinoma, figures 206 and 207.

Site.—Round-cell sarcoma: Periosteum, bone, lymphatic glands, subcutaneous tissue, testicle, eye, ovary, kidney, lungs, and intermuscular septa.

Spindle-cell sarcoma: Subcutaneous tissue, fasciæ, intermuscular septa, periosteum, interior of bones, eye, antrum, breast, and testicle.

Giant-cell sarcoma: Lower and upper jaw (alveolar processes), lower end of femur, and head of tibia.

Melanotic Sarcoma (*Melanosarcoma*).—Pigmentation may occur in any variety of sarcoma, and is frequently due to hemorrhage, followed by alteration in the hemoglobin and pigmentation. In certain forms of sarcoma the abundance of pig-

ment can not be fully accounted for by presuming an antecedent hemorrhage; the tumor cells seem able to elaborate pig-

FIG. 224.—MELANOTIC SARCOMA SPRINGING FROM THE SUBCUTANEOUS OR POSSIBLY FROM THE PERIOSTEAL CONNECTIVE TISSUES.

The intensely dark slate color, almost black, is well shown. The infiltrating margins of the growth could be approximately outlined by the unaided eye on account of the intensity of the pigmentation. The submaxillary lymphatics were enlarged and were crowded by pigment cells. Histologically, the pigment was within and between the cells, and was scattered through the tumor at all points.

ment. These tumors may be brown or slate-colored, and in some instances are almost black. (See Fig. 224.) Sections show the pigment in and between the cells. The tumors are very malignant. Occasionally, the amount of pigment produced is sufficient notably to influence the skin, the mucous membranes, and sometimes the urine; the pigmentation of the skin may be intense, giving rise to a discoloration resembling that seen in Addison's disease.

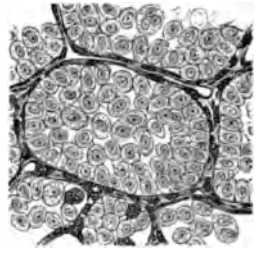


FIG. 225.—ALVEOLAR MELANOTIC SARCOMA.—(*Gould.*)

Endothelioma (*Plexiform Angiosarcoma*).—In this variety the cell nests are formed by proliferation of endothelial cells. The tumor is highly vascular, due either to preexisting or to newly formed

vessels, the walls of which become thicker, until at length the intervascular spaces are entirely filled up. It occurs in the subarachnoid and pia mater, and usually on serous surfaces. Occasionally, when occurring in the pia mater, the proliferated endothelial cells are aggregated into small, spheric nodules of a peculiar, shiny, pear-like appearance; it is then referred to as a *cholesteatoma*. Endotheliomata not uncommonly assume a distinctly alveolar type. The large, flat, endothelial cells springing from the serous surface, and occurring within distinct alveoli formed of connective tissue, afford a picture so closely resembling carcinomata that accurate differentiation seems at times impossible. This close resemblance has led to an unfortunate complication of names, such tumors being sometimes called *endothelial carcinomata*, and, again, *epitheliomata* of the serous membranes. Usually, a careful examination of a large number of sections will show areas distinctly sarcomatous. The shape, arrangement, and characteristics of the cells, associated with the poor development of the blood-vessels, point conclusively to the diagnosis of sarcoma. The author has recently had an opportunity to examine such a tumor springing from the tonsil or pharyngeal wall. The examination of a large number of sections has led the writer to believe that it is not impossible that some of these tumors may represent combined or associated processes; the coincidence of sarcoma and carcinoma in the same individual, or even in the same organ, occasionally occurs; the author has seen giant-cell sarcoma and scirrhus together in the female mamma.

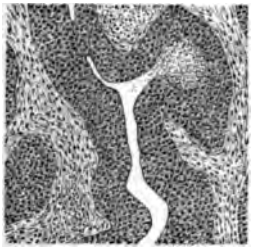


FIG. 226.—ENDOTHELIOMA.—(*Gould.*)

Psammoma (*Angiolithic Sarcoma*).—This is a peculiar tumor, containing sand-like masses and originating in the brain and its membranes, more particularly in the pineal gland and the choroid plexus; it contains fine, chalky, or calcareous concretions. These concretions show concentric lamination. Colloid or hyaline change may occur in or near the concretions; indeed, if the lime salts be cautiously dissolved by acids, a concentrically arranged hyaline matrix commonly remains. The occurrence of similar calcific deposits in tumors the tissues of which approach the adult type shows that the presence of calcareous deposit is not restricted to sarcoma, but may be seen in other growths developing in the areas indicated.

Chloroma.—This is another oddly formed cellular tumor; on

section, it presents a light green or dirty brownish color, which soon fades on exposure to air. Its cause is not known. It occurs chiefly in the periosteum of the skull.

Cylindroma.—This variety is produced by partial hyaline or mucoid degeneration of a sarcoma, or when there is a combination of sarcomatous and myxomatous tissue. The term is also applied to a variety of tumor of the epithelial type, known as *cylindroma carcinomatodes*, which is characterized by the formation of peculiar homogeneous spherules within the cell nests; it is probably a colloid degeneration.

Gliosarcoma.—Many sarcomata occurring in the eye are made up of cellular elements that resemble gliomata. The same is true of certain round-cell sarcomata. The term gliosarcoma is probably not justified. (See Glioma, p. 317.)

Sarcomata are particularly liable to secondary change. Areas in the tumor may show a decided disposition to complete the developmental tendency of connective tissue. As a result of this, true bone formation may occur—*osteosarcoma;* the term *osteosarcoma* has also been applied to sarcoma occurring in bone. It seems to the author, however, that the term should be restricted to those malignant growths showing the bony change just indicated. In the same way a sarcoma may show a modicum development of chondroid elements—*chondrifying* or *chondroid sarcoma*, or *chondrosarcoma*. Lipomatous sarcomata are rare. Sarcoma containing more or less mucoid tissue (*myxosarcoma*) are more frequent. In such tumors the change may be conspicuous in the intercellular substance, or it may be evident within the cells themselves. Conversion of the tumor cells into a structure resembling adult fibrous tissue has already been referred to in considering fibrosarcoma. Of the infiltrations to which the sarcoma is liable, calcification is the most common. Sarcomata containing calcific collections or concretions are sometimes called *osteoid sarcomata*, a name which is particularly objectionable as it resembles so closely *osteosarcoma*, a term applied with an entirely different meaning. (See above.) The presence of pigment in sarcomata need not be referred to at this point.

Fatty degeneration of sarcoma cells occasionally occurs. Sometimes the distinctly fatty areas may be conspicuous, and may be easily recognized as more or less irregular, yellowish patches. Cyst formation in the interior of sarcomata is occasionally observed; it is, however, a comparatively infrequent change.

As a result of the faulty development of the blood-vessel walls, areas of interstitial hemorrhage are not infrequent. These may assume the character of a suffusion, the blood infiltrating

between the tumor cells; more or less circumscribed areas of hemorrhage may also occur. When infection, ulceration, or superficial necrosis has removed the overlying skin or mucous membrane, sarcomata not uncommonly bleed, even profusely. With the lessened pressure that results from destruction of the overlying skin or mucous membrane the sarcoma not uncommonly protrudes as a fungoid growth, more or less narrowed at its base, and constituting a form of the *fungus hæmatoides* of the older writers. Infectious changes in the sarcomata may be evident. Extensive necrosis of the cells resulting from infection, and even gangrene of a large portion of the tumor, may occur. Such ulcerating surfaces may suffer saprophytic infection, and give off a penetrating, fetid odor. The patient's health may be profoundly influenced by the occurrence of infection; sapremia, true septicemia, or even pyemia sometimes develops.

DIAGNOSTIC FEATURES OF SARCOMA AND CARCINOMA.*

	Sarcoma.	Carcinoma.
1. Origin.	Entirely mesoblastic. (Connective-tissue type.)	Epiblastic and hypoblastic. (Epithelial-tissue type.)
2. Stroma.	Intercellular. Rarely forms alveoli.	Vascular connective tissue, which surrounds and forms the walls of the alveoli; these communicate with one another, and contain masses of epithelial cells.
3. Cells.	Granulation tissue or embryonic connective-tissue cells; shape and size vary.	Epithelial cells contained within alveoli; shape and size vary.
4. Intercellular substance.	May be present.	Absent, or merely fluid.
5. Vessels.	Embryonic in character. They are in direct contact with, or rather are composed of, the special cells, slightly modified, of which the tumor is composed.	Well developed; entirely contained within the connective-tissue stroma, and supported by the walls of the alveoli. Seldom in contact with the cells.
6. Spreads.	*Primarily* and *secondarily* by blood-vessels, rarely by the lymphatics.	*Primarily* by lymphatics, except in the later stages, when it may also spread by blood-vessels, in which case it spreads with very great rapidity. *Secondarily* by blood-vessels.
7. Secondary changes.	Chondroid, osseous, calcific, and pigmentary changes frequent.	Very rare.
8. Growth.	Not always continuous. Likely to be interrupted.	Rapid. Continuous.

* After Woodhead; modified and extended.

	Sarcoma.	Carcinoma.
9. Site.	Primarily in deep structures; always from connective tissue.	Primarily in superficial structures or glands; always from epithelium.
10. Heredity.	Seldom hereditary.	May be hereditary.
11. Capsule.	Primarily, pseudoencapsulated; later, infiltrates the surrounding tissue.	Never encapsulated.
12. Fat.	Rarely, if ever, contains fat.	Nearly always contains fat.
13. Age.	Occurs most frequently before middle life.	Most frequent after middle life.
14. Injury.	Not uncommonly follows injury, such as traumatism.	Rarely, a history of trauma, but most commonly follows prolonged irritation. Especially is this true of the superficial forms.

MIXED TUMORS.

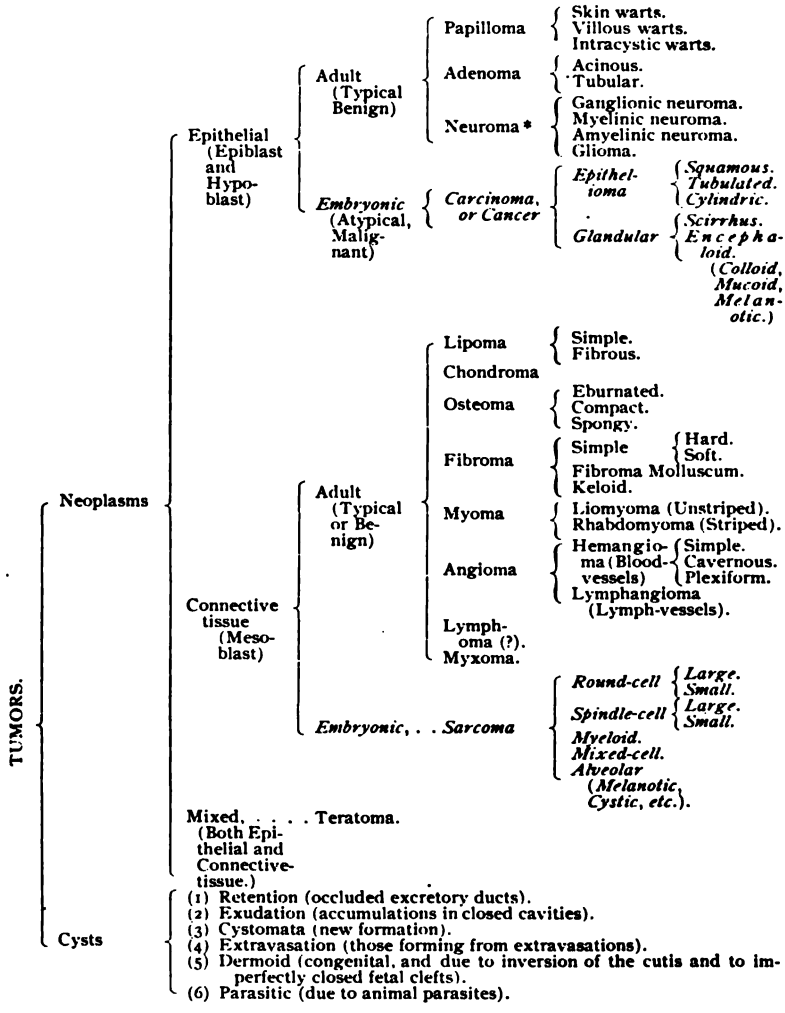
TUMORS COMPOSED OF BOTH TYPES OF TISSUE.

Teratoma.—This rare variety of tumor is composed of epithelial and connective-tissue types (adult and embryonic), and originates in rudiments derived from the three layers of the blastoderm (epiblastic, hypoblastic, and mesoblastic). Teratomata are congenital tumors, usually occurring in the sacral region (coccygeal tumors), the head and neck, or the abdominal cavity; they are occasionally observed in the kidney, ovary, and testicle.

They may be due to inclusion and imperfect development of one fetus within another, or to the abnormal development of the tissues of one fetus. They vary in size—may be small at birth, and may remain stationary or continue to develop. As evidence of fetal inclusion, the tumor mass may contain structures definitely suggestive of organs. Teratomata are frequently cystic; they sometimes recur after what was believed to have been complete removal; such recurring tumors are thought by some to possess a possible sarcomatous element. Dermoid cysts are, by some writers, classified with the teratoma. (See Dermoid Cysts, p. 361.)

TUMORS.

(Those printed in *italics* are malignant.)



CYSTS.

A **cyst** consists of a connective-tissue membrane or supporting wall lined by epithelium or endothelium, and forming a cavity the contents of which may be fluid or semifluid, uniform in composition, or made up of a mixture of similar or dissimilar substances.

* See foot note, p. 316.

When the wall of the cyst is passive and influenced by the retained or extravasated contents in a mechanical way only, the cyst is said to be *simple* or *unilocular*. When several simple cysts occur together, all arising from the same cause, and identical in structure, they are called *multiple cysts*. When one cyst springs from the wall of another and thus gives rise to a second or a third cyst, the process resembling proliferation, the resulting cysts are known as *proliferous cysts;* the cyst walls may be destroyed by pressure (reciprocal), and thereby many of the cyst cavities communicate. When the cysts remain distinct, they are spoken of as *multilocular*. When the cysts communicate, they are sometimes said to be *cavernous*. When the lining membrane of the cyst develops papillomatous masses, the process is called *proliferous* or *papilliferous*.

Classified by the cause and process of development cysts are said to be: (*1*) *Retention cysts;* (*2*) *exudation cysts;* (*3*) *cystomata;* (*4*) *extravasation cysts;* (*5*) *dermoid cysts;* (*6*) *parasitic cysts*.

1. **Retention Cysts.**—These include all cysts due to occlusion of the excretory duct of a gland with accumulation of the glandular secretion. Among the most common are: sebaceous cysts (wens); mucous cysts; salivary cysts (ranula); milk cysts (galactocele); seminal cysts (true spermatocele); nephritic cysts (see Cysts of the Kidney); cysts of the gall-bladder or biliary passages; pancreatic cysts (pancreatic ranula), etc.

The wall of such cysts is composed of condensed and thickened connective tissue, and the lining cells are of epithelium. The contents are derived from the functional activity of the gland structure, altered by absorption of a part of the fluid and by the degenerative changes that the cellular elements of the cyst wall may have undergone. Not uncommonly cysts of this class eventually contain none of the materials characteristic of the gland: *e. g.*, the fluid found in the kidney in hydronephrosis may contain no body characteristic of the renal secretion. (See Hydronephrosis.)

2. **Exudation Cysts.**—These embrace cysts arising from accumulation in closed cavities: that is, cavities not supplied by any excretory duct or analogous structure. Such cysts are typified in the accumulations in bursæ, tendon sheaths, the tunica vaginalis testis (hydrocele), canal of Nuck, etc.

The cyst wall is formed by thickened connective-tissue membrane lined with endothelium; the sac or wall may be calcareous, cartilaginous, fibroid, chondroid, or even osteoid. The contents are usually a clear, limpid, serum-like fluid, but the fluid may be viscid or semigelatinous, or cysts may contain

solid bodies resulting from changes in the wall and desquamation or exfoliation into the cavity.

3. Cystoma (*hygroma* or *hydroma*) is a cyst resembling the preceding, except that it is of new formation. The wall is of mesoblastic origin, lined by a flattened layer of connective-tissue cells (endothelium). The contained fluid is usually clear, straw-colored, slightly albuminous, and of low specific gravity; rarely, the fluid may be colored, cloudy, or, as a result of hemorrhage, grumous and possessing a dark, chocolate color. As to site, cystomata are most frequent in the neck (hydrocele of the neck) and in the axillæ (hydrocele of the axilla); although infrequent, they have been observed in the subcutaneous structures elsewhere—back, belly, and even the extremities. By reason of their being most commonly congenital, occasionally associated with macroglossia, and on account of their close resemblance to the dilated lymph-spaces of the frog, it is believed by many that they arise from dilatation of the lymph-spaces. The cysts have been classed with the lymphangiomata on the hypothesis that the process began as a dilatation of a lymph-space.

On two occasions the writer has seen cystomata of the liver; in both cases they were presumably congenital, and had been mistaken for sarcomata. One of the patients died from hemorrhage into the cyst, and the other from an intercurrent malady; both were children, aged three and six years respectively. It is not uncommon to find these cysts cavernous, with cavities of various sizes communicating with one another through one central space. The rule, as stated, that the specific gravity of the contained fluid is low, has occasional exceptions, as in rare instances the fluid may be as dense as the white of an egg, and so tenacious that it may not flow through an ordinary cannula introduced in tapping.

The most frequent site of a cystoma is in the ovary. Such tumors may be unilocular,—that is, made up of a single cyst cavity,—or they may be multilocular. The multilocular ovarian cystomata usually contain one, two, or more larger cysts and numerous smaller cavities. As a result of reciprocal pressure, there may be more or less destruction of the septa, and numerous cysts may communicate with one another, forming a cavernous cyst, within the cavities of which the fluid is lodged. Certain of the ovarian cystomata show papillary ingrowths, projecting from the inner membrane of the cyst wall as wart-like excrescences, which may be small or scarcely recognizable, or, on the other hand, may form large accumulations within the cyst cavity. As a rule, papilliferous cystomata are multilocular; less commonly they are unilocular. The lining membrane of ovarian cystomata

is usually composed of columnar epithelium, which in some cases may be of the tall variety. Ciliation is rare. External to this, the wall is composed of fibrous connective tissue, which may contain myxomatous elements, and at times masses of gland tissue. In the presence of the latter element the tumors are called *cystadenomata*, and are usually papilliferous.

As a rule, the ovarian cystoma is the largest cyst with which we have to deal. Dr. Elizabeth Reifsnyder has reported the removal of an ovarian cyst containing 88 quarts of fluid and weighing 169 pounds; the patient weighed but 77 pounds. The tumor was unilocular, the empty sac weighing 6½ pounds.

4. Extravasation Cysts.—This variety of cyst is formed around distended or ruptured vessels, or in areas of hemorrhage, and may occur in any tissue. *Hematocele*, or any form of *sanguineous cyst*, is properly classed with this group. The cyst wall is usually thin, and its inner surface smooth; but the reverse may be true. In rare cases the interior of the cyst—the wall—may be fasciculated. The cells lining the cavity are endothelial. Cysts occasionally occur through the extravasation of fluids other than blood; the accumulation of urine in the perineum, following rupture of the urethra, is a type of such cysts.

5. Dermoid cysts are always of congenital origin, and arise as the result of cutaneous inclusion, or in consequence of the inclusion of a blighted ovum. The wall may contain all the elements of the cutis, may be thick or thin, and not uncommonly shows a slight growth of hair; the cells lining the interior of the sac are, of course, epithelial. The contents are usually sebaceous matter and a varying amount of hair; occasionally, teeth are found. When situated in the ovary, testicle, brain, eye, throat, or abdominal cavity, developing bone or cartilage may be contained within the cyst cavity; these distinctly connective-tissue products indicate the possibility of such cysts arising from fetal inclusion. Occasionally, dermoid cysts contain fat the melting-point of which is below the normal temperature of the body. The author examined one such cyst. The tumor had evidently developed in the region of the ovary; the wall was so dense and calcareous that a saw was necessary to open the mass. The temperature of the body was still comparatively high, and the oily, fluid contents, which flowed from the interior of the cyst, immediately congealed on coming in contact with cold water. A similar tumor of the ovary has been described by Thoma. Dermoids containing distinct connective-tissue bodies, such as cartilage and bone, are termed *compound dermoids*, thereby distinguishing them from dermoids containing no connective-tissue elements; the

latter are called *simple dermoids.* The most common sites are near the orbit, the root of the nose, the angle of the jaw, the floor of the mouth, around the sheath of the carotid vessels, near the anus, and the sacrococcygeal and ovarian regions.

6. Parasitic Cysts.—When any animal organism capable of surviving in the tissues gains ingress, a cyst is likely to ensue; some such parasites inevitably give rise to cysts, others not always. *Trichinæ*, when settled, develop a small cyst that rapidly becomes calcareous. (See p. 198.) *Coccidia* invading the liver induce a similar condition. (See p. 193.) The most important parasitic cyst in man, so far as our present knowledge goes, is the *hydatid.* This cyst arises as the result of the lodgment of the larvæ of the tænia echinococcus in the tissues. The embryo is first converted into a cyst containing a clear fluid. The wall has two layers of its own, to which is added a layer resulting from the reaction of the surrounding elements. From the inner layer of the cyst—the endocyst—buds are developed that constitute the daughter cysts; other cysts develop in a similar way from the daughter cysts, and constitute what are known as granddaughter cysts. These cysts are, therefore, proliferative. The fluid of the cyst is usually nonalbuminous, slightly saline, and clear; its specific gravity is less than 1010, and it may contain sugar. Such cysts are likely to become inflamed, to suppurate, or to rupture, all of which terminations are unfavorable. If the parasite dies, the cyst may inspissate. It is not an exceptional thing to find these inspissated cysts in the liver; the contents are usually putty-like, occasionally crumbly, and frequently contain the hooklets. Inspissation represents a cure, but, unfortunately, other terminations may occur; the cyst may rupture into a closed cavity, as one of the serous cavities; rupture externally or into a bronchus or other hollow viscus occurs. A most dreaded termination is suppuration. (For consideration of the forms of hydatid cysts, diagnosis, and demonstration of hooklets, and for illustrations, see pp. 206 to 209.)

Site.—Liver, 46 per cent. of the cases, ovary, uterus, mamma, brain, testicle, kidney, lung, bones, muscles, serous membranes, general connective tissues.

Cysticercus Cellulosæ.—The larval form of the tænia solium induces small bladder-like cysts, which may be widely distributed. In the pig, the usual intermediary host, the cysts are about the size of a pea, and may be scattered throughout the tissues, producing a condition commonly known as "measled" or "measley" pork. (See p. 204.) In man the cysts occur in the muscles, brain, and spinal cord; occasionally, the cysts may be recognized by the ophthalmologist in the chambers of the eye.

CHAPTER VIII.

INFECTIOUS GRANULOMATA.

The infectious granulomata include a series of granulation tumors, all of which are due to some form of bacterial life, although in syphilis the precise etiologic factor has not been definitely determined. The infectious granulomata include syphilis, tuberculosis, glanders, actinomycosis, and leprosy. These are all characterized by the development of a peculiar mass formed of variously known cellular elements resulting from accumulation of leukocytes and proliferation of the connective tissue. The resulting tumor is known as a *granulation tumor*, as a *specific inflammatory tumor*, as an *infectious granulation tumor*, etc. The etiologic factor is found in the tumor, and, when the disease is communicable to lower animals, these granulation masses contain the cause, which, if transferred to a susceptible animal, will give rise to the disease.

SYPHILIS.

Cause.—While all the clinical and pathologic data point to the disease being due to a specific microorganism, this fact has not as yet been positively demonstrated. Lustgarten has demonstrated the presence of a bacillus closely resembling the tubercle bacillus, in that it stains similarly by the anilin stains; but it is more readily decolorized by acids. It is about the size of the tubercle bacillus,—if anything, it is a little more slender,—and very closely resembles the smegma bacillus. (See Bacillus of Syphilis, p. 189.) As the disease is not communicable to lower animals, experimental evidence proving the pathogenic activity of the germ is not forthcoming.

Syphilis may be **acquired** or **congenital.** In the *acquired* form it is essentially a venereal disease, in that it is rarely transmitted except by coitus. Infection by other means occasionally occurs, and constitutes the so-called "syphilis of the innocent." The disease may be transmitted by kissing. An abrasion on the hand coming in contact with infection-carrying discharges, as in midwifery, may give rise to a chancre. The disease has been transmitted by vaccination, although this form of infection

must now be very rare; syphilis has been similarly inoculated in tattooing.

Congenital syphilis may be transmitted (1) by a syphilitic father; (2) by a syphilitic mother, who was syphilitic prior to conception, or who acquired syphilis at the time of conception or during gestation. When syphilis is transmitted to the child during delivery, the condition is one of acquired syphilis.

Morbid Anatomy.—The initial lesion of syphilis—the **chancre**—consists essentially of a new growth in the skin or mucous surface, followed by hyaline degenerative and necrotic processes, which usually terminate in ulceration. The connective tissue of the skin is infiltrated by small round-cells, which even invade the subcutaneous structure. In these masses of lymphoid cells will be found epithelioid cells, and, occasionally, a few giant-cells. This converts the mass into a hard, almost inelastic, indurated area. The extreme hardness of the mass is one of its most characteristic features, and hence the term "hard chancre" is often used to differentiate the lesion from ulcerative or inflammatory processes arising from other causes. When the process is associated with a mixed infection inducing more or less rapid liquefaction of the proliferate, induration may be inconspicuous, or may even be absent. The view that absence of induration is, to a certain extent, dependent upon the character of the tissue infected, does not seem to be tenable, as so distinguished an observer as Hutchinson maintains that any tissue may suffer induration, and that chancre in any area is commonly associated with the occurrence of this phenomenon. The blood-vessels undergo sclerosis, and cutting-off of the blood supply results, which condition may lead to liquefaction necrosis of the epithelium above; an ulcer does not always form, liquefaction necrosis does not always occur, and occasionally a chancre will be observed in which the epithelial covering remains unbroken. When ulceration does occur, it is a cup-like or scooped-out ulcer, and is not undermined, and it is not likely to be sloughing or phagedenic. With the subsidence of cellular infiltration, repair begins; the cells are removed, and gradually resolution is accomplished.

Associated with the initial lesion, the nearest anatomic lymphatic glands show the alterations incident to infection. In some instances the local lymphatic involvement usually manifested during the activity of the initial lesion escapes observation, or, possibly, it is not present. During this process the lymphoid structures proliferate and become more or less edematous, thereby bringing about induration and considerable swelling in the affected glands. The glands involved are those functionally nearest the

initial lesion. If pyogenic bacteria gain ingress through the ulcer or by other routes, the glandular swelling and hyperplasia may terminate in suppuration; when suppuration does not ensue, which is usually the case, the infiltration and induration gradually subside. Following this, a stage of apparent quiescence ensues, which, as in other infective diseases, constitutes the period of incubation. This persists for from ten days to six months; the extremes given are unusual, the secondary phenomena commonly manifesting themselves in about six weeks. The lymphatic glands (it is probable that all the lymphatic glands participate; certainly, all that can be discerned from the surface) show a varying amount of induration and swelling; not, however, associated with suppuration. Syphilis has now passed into the secondary stage, and multiple cutaneous lesions occur; these are clinically important, but pathologically they are not essentially different from many skin lesions that arise independent of syphilis. Syphilitic eruptions are commonly characterized by their polymorphism and their symmetric distribution. The exanthem is not restricted to the skin, but appears also on the mucous membranes. The cutaneous and mucous lesions of secondary syphilis usually involve the superficial layers of the mucosa and the skin, rarely extending sufficiently deep to justify their being considered ulcerative. During this stage, usually at its beginning, there is commonly malaise and slight fever (*syphilitic fever*). The intensity of the infectious processes may be further indicated by the occurrence of inflammation of the iris or retina, joint and bone pains, and alopecia. A more or less conspicuous lesion of this stage is a so-called *mucous patch*. This appears on the mucosa of the mouth, on the genital mucous membranes, and upon the anal mucosa; a similar, if not identical, lesion is seen on the skin near the anus. These patches result from superficial exfoliation of the corium and of part of the Malpighian layer, with degenerative and proliferative changes in the latter, and from a slight infiltration of the underlying connective tissue. The round-cell elements present in the corium are never so abundant as in the initial sore; the resemblance, however, is striking, and the essential infectious nature of the lesion is further indicated by the fact that the etiologic factor is abundantly present, and that the disease may be as readily communicated by the discharges from such surfaces as from the initial lesion.

The tertiary lesions, which are pathognomonic, are the **gummata, syphilomata,** or **granulation tumors** of syphilis. Gummata are developed as masses of embryonic cells, containing lymphoid and epithelioid cells, with a very slight amount of tra-

beculæ; occasionally, giant-cells are present; hyaline degeneration, followed by fatty changes, may convert the center into a caseous-like material. The process of caseation is accompanied by syphilitic disease of the blood-vessels of the area, cutting off the nutrition to the center of the mass. Rarely, a secondary infection may give rise to suppuration. When superficially situated, necrosis of the overlying tissue—skin or mucous membrane—leads to infection and suppuration. With destruction of the overlying tissue there commonly appears a central necrotic core, which separates slowly. In the absence of treatment the necrosis (ulceration) extends peripherally, and in some instances in depth as well. At the present time necrosis and ulceration are rare in recognized gummata. A gumma varies in size from a purely microscopic body to a mass five, ten, or even fifteen centimeters in diameter, the latter commonly resulting from confluence of smaller primary gummatous areas. At first the gumma is hard; later, with beginning degenerative change in the newly formed elements, it may become so soft as to resemble a cold abscess or as to manifest pseudofluctuation resembling a cyst. Gummata are sometimes multiple, occurring simultaneously in a number of the tissues and organs. A single nodule is, however, the rule. Gummata occur in nearly all the tissues, and are most frequently observed in connection with the periosteum, particularly that of the cranial bones. Frequently, they are situated in the subcutaneous tissue; they also occur in the liver, kidney, and lung, and even in the heart. The brain is not infrequently a site. In the mucous membranes—particularly of the larynx, trachea, nose, and pharynx—and in the rectum extensive tissue destruction may result. With ulceration, or even in its absence, the subsequent cicatrization may give rise to narrowing of those tubes the walls of which are involved. Such strictures are seen in the rectum and in the trachea.*

TUBERCULOSIS.

Cause.—The *bacillus of tuberculosis* is the essential etiologic factor in all the lesions of this disease. (For description see p. 180.) Tuberculosis occurs in man and in other warm-blooded animals, although several of the latter are very rarely attacked; particularly is this true of the horse and the ass. Of the races, it would seem that the Indian and negro are particularly suscep-

* An illustration showing syphilitic stenosis of the trachea will be found in the chapter on Diseases of the Organs of Respiration, part III.

tible to the disease. The tuberculosis seen in fowls (*avian tuberculosis*) presents lesions that resemble the tuberculosis of man. There are differences, however, which, until recently, have been considered sufficiently distinctive to differentiate the two diseases. The dissimilarity of the two organisms has already been pointed out. (See p. 182.) Should subsequent investigations confirm the claim of conversion of the bacillus of human tuberculosis into the bacillus of avian tuberculosis, we would then be forced to admit that the disease as seen in fowls is but a modified form of the same process occurring in men. Spontaneous avian tuberculosis occurs most frequently in the liver, the lungs being rarely, if ever, primarily involved. Degenerative and necrotic processes are less conspicuous, or may be absent.

Prenatal Tuberculosis.—While there is no doubt that instances occur in which the fetus is infected *in utero*, and that tuberculosis can be communicated through the placenta, still such cases are extremely rare. What is inherited, and what is transmissible from generation to generation, is that peculiarity of tissue, or peculiarity of soil, that favors the development of tuberculosis; thus, it is constantly observed that tuberculosis, or this tubercular proclivity, is transmitted from parent to offspring in an almost unbroken line. As a further evidence of the transmission of tissues possessing an increased susceptibility to a given disease, it has been observed by physicians associated with life-insurance companies that a child resembling a tuberculous parent is more likely to develop the disease than a brother or sister whose physical characteristics follow more closely those of a nontuberculous progenitor.

Other Methods of Infection: 1. By Inoculation.—Inoculation is represented in the postmortem nodule, *verruca necrogenica* of Wilks. The author has had an opportunity to observe a rather extensive local tuberculosis of the tendon sheaths of the hand and wrist, resulting from infection of an open wound upon the thumb; the patient had nursed a son suffering from pulmonary tuberculosis, and during his illness had accidentally wounded her thumb. The wound was slow to heal, and even before its disappearance, tuberculosis of the adjacent tendon sheath developed; later, the tuberculous process extended to a number of tendons in the wrist, eventually following the course of these structures in both the dorsal and palmar tissues.

2. Infection through the air, as the result of inhalation of dust containing pulverized sputum laden with bacilli. Recent observations and experiments seem to indicate that infection through the air by means of dust is less frequent than infection by the

small droplets of infected sputum ejected during attacks of coughing.

3. Infection through Food.—This is particularly likely to occur through milk and meat, by reason of the wide zoologic distribution of tuberculosis.

4. The danger of infection is increased by any condition that reduces the resistance of the individual, by the presence of other forms of infection or of inflammation of the mucous membranes, and during convalescence from other diseases. Unfavorable hygienic surroundings, crowding, and similar conditions, favor the chances of infection.

Morbid Anatomy.—In order to induce infection the tubercle bacillus must gain access to the connective-tissue structures; as

FIG. 227.—DIAGRAM OF THE STRUCTURE OF A TUBERCLE; A PURELY THEORETIC IDEA, RARELY DEMONSTRATED.—(*Gould.*)

soon as this occurs, in susceptible individuals, proliferation of the fixed connective-tissue cells takes place, producing the so-called epithelioid cells of tubercle. The endothelium of the capillaries probably participates in the process of proliferation; into this structure leukocytes wander, and invade the connective-tissue matrix, the leukocytes constituting the lymphoid cells of the tubercle. The foregoing explanation of the origin of the epithelioid cells has not been demonstrated beyond the possibility of a doubt; the hyaline leukocytes resemble, in many particulars, the so-called epithelioid cell, and the presence of the other usual mononuclear leukocyte is not incompatible with the view that the epithelioid cell is really the hyaline leukocyte. More or less serous infiltration of the tubercle probably occurs, and in recent tubercles properly fixed, or in older tubercles showing active

peripheral extension, a varying amount of fibrin-forming bodies may be present. If the cellular elements be crowded, and the nutrition not abundant, the proliferated epithelioid cells may undergo incomplete segmentation, the nuclei dividing but the protoplasm of the cell remaining intact, thus giving rise to the giant-cell. It is also maintained that the packing of the epithelioid cells may lead to breaking-up of the cell margins, producing, thereby, a giant-cell by confluence of ordinary epithelioid elements. The giant-cells seen in tubercles and possibly in other chronic infections, differ in some respects from many of the large multinucleated cells, ordinarily called giant-cells, seen in tumors, reparative processes, etc. There is probably nothing absolutely characteristic or immutably constant in this difference, which is, however, usually recognizable and worthy of note. The nuclei are most frequently peripherally located, and not uncommonly are grouped toward one side of the cell. Possibly as a result of necrotic changes going on in tubercles, the chromatin does not possess a strong affinity for the basic dyes. The intensity of the staining, however, varies within wide limits. The presence or absence of giant-cells is largely dependent on the condition of crowding and on the facilities afforded for complete cell division ; tubercles without demonstrable giant-cells are not infrequent. The fibrous tissue of the part constitutes a reticulum, or network, in which the added cellular elements just described are matted ; the process, therefore, resembles an inflammatory reaction of the tissues, an attempt to limit the dissemination of the infecting agent. When necrotic and degenerative changes give rise to nuclear fragmentation and to breaking down of the cell protoplasm, the connective-tissue reticulum is usually the last structural element to disappear.

The mass previously described varies in size, being rarely larger than a pinhead (one or two millimeters), although it may be much larger ; as a rule, a number of these develop conjointly, and become confluent. The tubercle large enough to be seen by the unaided eye contains, as a rule, many small tubercles, such as that described. By the changes already noted, the capillary blood supply is cut off from the center, leading to the occurrence of necrotic and degenerative processes ; owing to the specific action of the bacillus, or, more properly, of the bacillary products, caseation ensues. In the beginning of this process granular and fatty changes occur in the cell protoplasm, the cell outlines become indistinct or disappear, and the nuclei shrivel and disintegrate ; the nuclear fragments often retain their affinity for basic dyes long after the structurally perfect cell has disap-

peared. The caseous area produced by the foregoing changes may follow the peripheral extension of the process until two or more tubercles join by confluence into the formation of a single mass. Caseation may be accompanied by liquefaction, coagulation, or hyaline necrosis; eventually, the mass is converted into a yellowish nodule of structural detritus, the so-called **yellow tubercle**; prior to the stage of softening the mass was referred to as a **gray tubercle**; where a number of these run together, the collection shows a decided tendency to evacuate itself by discharge through the most feasible route, leaving behind a

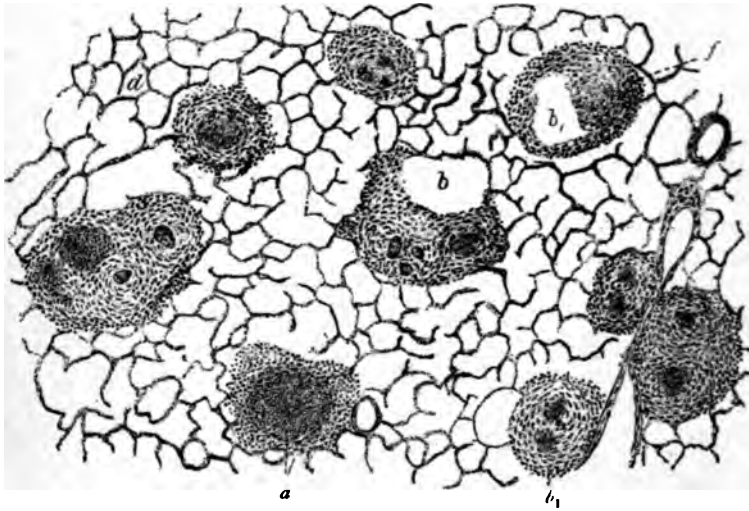


FIG. 228.—ACUTE DISSEMINATED TUBERCULOSIS OF THE LUNG.—(*Schmaus.*) × 40 diameters.
a. Tubercle undergoing caseation. Just below the letter *b* are two tubercles: the one on the left contains three giant-cells; the one on the right shows beginning caseation. b_1, b_1. Tubercles. *c*. Nodule containing at least four tubercles; two show beginning caseation and two contain giant-cells. *d*. Alveolus. To the left of *e* is a blood-vessel. *f*. Area of beginning caseation. Other tubercles are also shown.

cavity or ulcer. If not in all, certainly in a large percentage of the cases, dissolution of the tubercle is brought about through a secondary infection by the organisms of suppuration. The tuberculous ulcer and abscess are more commonly, particularly in the respiratory organs, hastened to their full development by this secondary infection. This terminates the process of softening, and is an unfavorable ending of the tubercular process.

Healed-in, Latent, or Quiescent Tuberculosis.—In favorable cases there is an attempt to limit the process by the development of a dense wall surrounding the tubercular area, through

which any fluid that results from the degenerative changes may be partly absorbed, leaving behind the caseous detritus, containing not uncommonly tubercle bacilli; into the fibroid capsule and caseous material calcareous infiltration may occur, forming a stone-like mass, in which the tubercular virus may be destroyed or indefinitely stored. Sometimes the fibroid change (*fibrosis*) may be conspicuous and the calcareous infiltration but slight; in other instances the calcific matter may obscure the whole mass. The tubercle bacilli contained within such nodules may retain their viability, and hence their pathogenicity, or, in the course of time, may be no longer demonstrable. At first the organism stains with its characteristic activity—a reaction that becomes less and less manifest, and eventually disappears, so that, in old tubercles, under suitable conditions, the organism may be destroyed, or at least not demonstrable, and the degenerated contents of the mass may be no longer infective. During the latter stages in the development of this body it is known as a **quiescent tubercle** or tubercular area. Such "healed-in" tubercles may remain inactive or may, if they contain viable bacilli, manifest recrudescence. The length of time during which the bacilli retain their pathogenic activity can never be foretold; therefore, a quiescent tuberculous area must always constitute a menace to health, as, under favorable conditions, the bacilli may at any time be rapidly disseminated, giving rise to miliary tuberculosis.

Secondary Infection in Tuberculosis.—Park (Mütter lectures) lays particular stress on the mixed infections in tuberculosis. In ordinary forms of tuberculosis the symptoms are largely due to the pyogenic infection of tubercular areas: thus, a tubercular or caseous abscess may be converted into an abscess containing pus by ingress of pyogenic bacteria. When saprophytic organisms also find lodgment, the process is likely to be attended with more marked phenomena than when the pyogenic organisms alone are present.

Extension of Tuberculosis.—Tuberculosis develops as an initial lesion, inoculation, or point of primary invasion, from which local or general extension may occur. The necessity of a recognizable initial lesion is not always to be insisted upon, for when a guinea-pig is fed tubercle bacilli, infection of the lymphatic glands of the mesentery may occur without any recognizable lesion in the alimentary canal. Tuberculosis of the mesenteric glands, as seen in children, is similarly explained, particularly when we take into consideration the frequency with which milk contains tubercle bacilli. The local tuberculous lesion seen in the lymphatic glands of the neck must have re-

sulted from infection through the oral cavity, possibly the tonsil, without there having been any history to indicate a past or associated initial lesion of the mucous membranes at the point of ingress. The possibility, however, of superficial initial lesions has already been pointed out. (See p. 367.) Tubercle bacilli may enter the body without the production of any recognizable superficial lesion. The occurrence of tuberculosis of the body of a vertebra, or of primary tuberculosis of a joint, without other evidences of the disease, must indicate such a possibility. The fact that a local lesion is not produced, and that bacilli may apparently pass into, and travel by, the circulation, eventually inducing tuberculosis in distant parts, indicates that the induction of a primary tuberculous nidus is dependent upon factors other than the mere presence of tubercle bacilli. These factors are probably the lessened resistance of certain tissues, or, we might say, greater susceptibility, and the occurrence of points of least resistance. The latter may be produced by associated lesions or injury. The fact that certain tissues possess a higher degree of susceptibility to tuberculosis is indicated by the frequency with which the disease occurs in the lung, bones, and lymphatic glands. The presence of such heightened susceptibility also indicates a relative immunity in other tissues: for example, the muscles, in which typical tuberculous lesions are rare. From the initial or primary lesion of tuberculosis extension may occur by one of the following routes:

1. *By the Blood.*—A tuberculous lymph-gland or nodule in the lung, bone, or elsewhere, may discharge its contents into a vein; a caseous peribronchial lymphatic may rupture into a pulmonary vessel, artery, or vein; the intravascular presence of tubercle bacilli may result from tuberculous deposits emptying into the thoracic duct or into a lymph-vessel that drains directly into a vein without filtering its contents through an intercalated gland. It is not improbable that in the blood, as an infected embolus, the bacilli may increase in number, and may eventually lodge in a capillary, or attach themselves to the vessel wall (mural implantation) and give rise to the development of a tubercle. Such dissemination is likely to be general.

Dissemination of tubercle bacilli by means of the blood usually results in the wide-spread distribution of the organism, followed by the eruption of a large number of tubercles in various organs. Such a condition is called general miliary tuberculosis. The wide-spread dissemination of the lesion is associated with more or less marked febrile and other toxic phenomena. The tubercles rarely attain any considerable size, as the patient commonly dies

before sufficient time has elapsed. In other instances the amount of infectious material disseminated was evidently small, giving rise only to a few tubercles scattered here and there through the viscera. Under such circumstances the patient may survive long enough for the tubercles to attain considerable size, and even to caseate. Whenever there is a general miliary tuberculosis such as just indicated, there is reason to believe that a primary caseous nodule has communicated in some way with the general circulation. Often a most careful postmortem will fail to show the primary lesion. The author recalls a case of general miliary tuberculosis involving nearly all the viscera, in which a most careful search was about to be abandoned when the primary nodule was discovered in the anterior part of the body of a dorsal vertebra. Subsequent inquiry elicited the fact that the patient had had, a few weeks before admission to the hospital, a severe fall, which strained his back, and to which he attributed his illness. The slight inflammatory changes that surrounded the nodule indicated that possibly, indeed probably, the injury had caused it to break into the surrounding cancellous bone and favored the dissemination of its contained infectious matter. The possibility of disseminating tubercle through the blood-stream as the result of incomplete operative procedure has been pointed out by many surgeons. The breaking up of a tuberculous area without at the same time completely eradicating infection may be followed by general dissemination of the poison, miliary tuberculosis, and death.

2. Another means of extension is by the *lymph-stream*. This is illustrated in the tubercular glands of the neck in children, which result from infection through the tonsils and through diseases of the teeth, gums, and oral mucosa; the same method of spread may be illustrated by the tubercular processes along the lymph-system, following tubercular ulceration of the intestine.

3. In addition to the lymph and blood, the bacilli may follow the *course of other fluids*. Thus, tuberculosis of the alimentary canal may be secondary to tuberculosis of the respiratory passages, and may be due to the swallowing of bacilli-laden sputum; tuberculosis of the bladder or tubercular abscess of the perineum may be secondary to tuberculosis of the kidney.

Locally, tuberculosis may spread by *continuity and contiguity* of tissue; this may occur even against the ordinary course of fluid currents, as in tuberculosis of the ureter, which may be secondary to tuberculosis of the bladder; tuberculosis of the prostate may be secondary to tuberculous processes in the rectum or in other adjacent structures; tuberculosis of the intra-

cranial structures may be secondary to tuberculosis of the middle ear or mastoid cells, or of the frontal sinuses.

Site of Tuberculosis.—One of the most common sites is the lung; following this in frequency, tuberculosis of the joints, bones, and lymph-glands come next in order; these are followed by tuberculosis of the mucous membranes other than the lungs, tuberculosis of the serous membranes, tuberculosis of the skin, tuberculosis of the spleen, tuberculosis of the liver, tuberculosis of the brain, tuberculosis of the generative organs, and tuberculosis of the heart and voluntary muscles, in the order given.

Tuberculosis of the organs will be further considered in part III. The only form of local tuberculosis that will be described at this point is lupus.

Tuberculosis of the Skin (Lupus).—This condition usually begins as a lymphoid infiltration following the course of the vascular loops in the corium. The process slowly extends by the development of outlying tubercles that coalesce with the older nodules. The fully formed tubercle in lupus may be, and indeed is, usually structurally identical with tubercles as seen elsewhere. Sometimes the miliary tubercle is quite atypical in the skin, and in the absence of the bacilli a satisfactory diagnosis can not be made. In the ulcerative form of lupus (**lupus exedens**) the coalescence of tubercles in the corium, and even for some distance in the subcutaneous tissue, associated with the obliterative changes in the capillaries followed by caseation, leads to necrosis of the overlying derma and the formation of an ulcer. Occasionally, superficial necrosis does not occur, and hence ulceration is absent. In such cases the infiltration commonly shows more fibrous tissue than in the ulcerative form of the lesion; the skin is slightly raised, and is usually somewhat more adherent than normal; occasionally, outlines of caseous masses can be detected beneath, even when superficial necrosis does not follow. This form of cutaneous tuberculosis is known as **lupus nonexedens.** It is probable than cutaneous tuberculosis results from local inoculation; the author has seen one well-marked and protracted case of lupus that followed vaccination, and two cases of extensive cutaneous tuberculosis in which the lesions followed the application of the actual cautery, the ulcerative process having been purposely prolonged for its so-called alterative action. Lupus is a particularly chronic and intractable disease, but may be associated with, or followed by, more general tuberculous dissemination.

PSEUDOTUBERCULOSIS.

A further study of the chronic infections will reveal the fact that other organisms may induce lesions not to be differentiated histologically from the tubercle developed at the point of lodgment of the tubercle bacillus. Not only may the nodules closely resemble those of tuberculosis, but the organism present may require a detailed study in order definitely to establish the fact that it is not the tubercle bacillus. It is not possible to go into all the pseudotuberculous conditions or tuberculoid processes; the following, however, may be mentioned:

There have been obtained from milk and milk products, from hay, from the dung of lower animals, and from other sources, bacteria that stain like the tubercle bacillus, and that give rise, after inoculation, to nodules closely resembling true tubercles. It is said that in many of these tuberculoid processes giant-cell formation and caseation are inconspicuous or absent. Cultivation of bacteria renders differentiation possible. In sheep certain animal parasites (worms and ova) produce pulmonary lesions not unlike those of tuberculosis. The horse suffers from a pulmonary lesion that is associated with the presence of mycelia, and that closely simulate tuberculosis. Aspergillosis also resembles tuberculosis (see later). Little is known of the foregoing infectious processes, so far as man is concerned; some of them have undoubtedly occurred in man, and their occasional occurrence in a lower animal renders the likelihood of infection in man always worthy of consideration. It is not impossible that many cases of atypical or irregular tuberculosis, if carefully studied, would be found to be instances of pseudotuberculosis.

GLANDERS.

Glanders is a bacterial disease occurring in horses and asses, but communicable to man, and is due to the *bacillus mallei.* (For description of bacillus see p. 179.) Glanders in man occurs in two forms: (*1*) *Localized, circumscribed,* or *chronic glanders,* or *farcy;* (*2*) *general, disseminated, acute,* or *septicemic glanders.*

1. **Localized Glanders.**—Infection by the bacillus mallei, involving the skin and adjacent lymph-glands, called *farcy;* when the mucous membranes are affected, the condition is spoken of as *glanders;* so that at one time it was customary to describe acute and chronic glanders and acute and chronic farcy. It is now recognized that glanders and farcy are due to

the same cause, and that there is little essential difference between the pathology of the "farcy bud" and the glanders nodule. By some the local or chronic manifestation of infection with the bacillus mallei is called glanders, while the term farcy is applied to the general, disseminated, acute, or septicemic glanders.

It does not seem probable that the organism can gain ingress except through an abraded or wounded surface, although experiments are not wanting to show that the bacillus may be forced into the skin when applied by inunction with even slight friction. As communicated to man, the disease usually comes from the horse, and is therefore most common in hostlers and those employed around stables, etc. When the glanders bacilli localize in the subcutaneous or submucous tissue, there develops a small nodule, rarely as large as a pea, made up of an almost pure lymphoid infiltrate, containing a few giant-cells and the characteristic bacilli. By necrosis, the mucous membrane or the skin breaks down, and the resulting ulcer is usually foul, without any abundant discharge; when a number of the ulcers are located near one another, they not uncommonly show a decided disposition to become confluent, forming irregular serpiginous ulcers. There is likely to be lymphangitis, extending to the neighboring lymph-glands, which may become large and may suppurate. This constitutes the so-called **chronic glanders or chronic farcy.**

2. Acute Glanders.—In the acute form the condition more closely resembles miliary tuberculosis in the rapid dissemination of the poison and the wide-spread distribution of the lesions. Weichselbaum describes a case of acute glanders in which, without any apparent initial lesion, there occurred throughout the viscera multiple glanders nodules, which were not diagnosticated during life; at the postmortem a thrombus was found in one of the meningeal veins, and from this, no doubt, had arisen infected emboli, which had given rise to the general dissemination of the lesion. In this condition the bacilli are found in the blood and in many of the discharges; multiple cutaneous eruptions are likely to occur; the larger joints may be implicated, as in other forms of septicemia; in the male the testicles may be involved. Multiple abscesses may occur throughout the body, closely resembling pyemia. Death usually occurs from exhaustion. This constitutes the septicemic form of glanders, and may occur (1) without any initial lesion that can be discerned; (2) it may be associated with an initial lesion that runs a rapid course; (3) it may terminate the chronic form of farcy or glanders, as already described.

The secondary changes that may occur in a farcy nodule resemble in some respects those seen in tubercles. Latent or "healed-in" nodules are not infrequent; they commonly show peripheral fibrosis and calcareous infiltration similar to that already described when considering "healed-in" tubercles. (See p. 370.) Such latent nodules are seen in lymph-glands and in the lung, and occasionally in other viscera. During the development of the farcy node interstitial and peripheral hemorrhages are not infrequent, and in the lung an associated pneumonia is usually present. The latter may be restricted to a small zone around the node or it may, as in tuberculosis, involve a large area of the pulmonary tissue, giving rise to alterations that closely resemble those of croupous pneumonia. The routes of infection and dissemination are practically the same as those already given for tuberculosis. The occurrence of multiple abscesses scattered through the body, containing staphylococci as well as the specific organism of the disease, is indicative of the pyemic character of the lesion. The erythematous, papular, phlyctenular, bullous, and pustular eruptions are also evidences of the general infection; they have led to confusion in diagnosis, the disease having been mistaken for measles, chicken-pox, smallpox, syphilis, etc.

ACTINOMYCOSIS.

Actinomycosis is a disease most common in the cow, where it is known as *clyers*, *wooden-tongue*, *big-jaw*, etc. The disease is due to the ray fungus, for a description of which see page 160. The fungus, in masses, is usually sufficiently large to be recognized in the discharges as small yellowish-white, white, or brownish-white tufts, varying from the size of a grain of sand to that of a pinhead; these, if picked out of the discharge and crushed between cover-glasses, may be stained and demonstrated as elsewhere described. The infection usually occurs through the mouth and pharynx, probably through some abrasion in the mucous membrane, or possibly through a diseased tooth. Chiari first described a case in which the primary infection was probably a mural implantation on the intestinal wall.

Morbid Anatomy.—Once the fungus secures admission to the connective tissues, there is engendered a granulation tumor containing large masses of lymphoid cells, a few epithelioid elements, and giant-cells very closely resembling in structure a tubercle: the lessened tendency to necrosis or caseation, however, permits these masses to accumulate and to become of considerable size, when, prior to the discovery of the cause, they

were not uncommonly mistaken for sarcomata. The size of the actinomycotic masses varies. The larger nodules, which may attain the dimensions of a fetal head, are not uncommonly honeycombed, resembling a trabecular structure, the stroma of which is formed from the connective tissue of the affected part. The irregular alveoli formed by the connective tissue are distended by inflammatory products containing the vegetable parasite. When occurring in bone or on the skin, the resemblance to sarcoma may be striking. Ulcers formed on the skin are crater-like, and discharge a clear, mucilaginous fluid, sometimes in large quantities. The local extension of the process is peculiar, in that it advances steadily, involving contiguous tissues, and does not appear to follow the path of least resistance, such as the course of a muscle, blood-vessel, or nerve, or the lymph-stream. Penetration of venous walls permits the formation of actinomycotic thrombi, which, becoming fragmented, give rise to emboli containing the specific organism. In Ponfick's case such a thrombus occurred in the jugular vein, and later embolic metastasis showed itself in the heart, lungs, spleen, and brain. Probably on account of the large size of the germ, dissemination by the lymph-stream is less common than by the blood supply. The actinomycotic nodules are prone to break down into material resembling pus; whether this pus-formation could occur independent of pyogenic organisms was for a long time a disputed point, but it is now generally admitted that actinomycosis may terminate in suppuration, resulting from the direct action of the fungus independent of other organisms.

Sites.—In over fifty per cent. of the cases in man the lesion is located in the tissues of the head and neck. The intra-abdominal organs are next in point of frequency, the lungs, tongue, and skin following in the order given. Actinomycosis has been observed in the generative organs, particularly in the Fallopian tube; the reported cases of actinomycosis of the female reproductive organs are of special interest, particularly when we take into consideration the fact that only about one-third of all the cases of actinomycosis occur in women. Actinomycosis is also seen in the medulla of long bones and in the cancellous tissue of small bones, and has been described in the mastoid cells and in the middle ear. Primary pulmonary actinomycosis has been observed; primary cerebral actinomycosis occurs, although cerebral actinomycosis is usually due to metastasis, the fungus reaching the brain from a local lesion elsewhere.

Mycetoma and Other Conditions Resembling Actinomycosis.—Mycetoma, or Madura foot, also known as "fungus

disease" of India, is an essentially chronic, slowly spreading, inflammatory process that affects the hand or foot. There is rapid proliferation of the connective tissues, with the formation of more or less typical granulation tissue, in which necrotic, degenerative, and suppurative processes occur; these lead, sooner or later, to the development of sinuses that discharge a serous or serosanguinous pus. In the *ochroid* or "*pale*" variety of the malady the discharge contains brownish-yellow or yellowish-white bodies, which resemble fish-roe. In the *melanoid* form the bodies discharged are black or brownish-black. The colored granules contain the specific organism, and if sown under suitable conditions, cultures are easily obtained; these resemble the actinomyces. In a case reported by Wright, the organisms present were believed to be hyphomycetes. While the bacteria found in actinomyces and Madura foot are apparently related, the two diseases show distinct clinical differences. Mycetoma is a disease of the hands and feet, frequent in hot climates, and remains always a local infection, without metastases; these peculiarities are not characteristic of actinomycosis. (For Description of the Organism see p. 162.)

ASPERGILLOSIS.

The term aspergillosis has been proposed for lesions produced by the *aspergillus fumigatus* (*hyphomyces*). The structural alterations induced by this organism resemble very closely those of actinomycosis. Little is known of the disease in man, although there is reason to believe that some of the cases of what appears to be pulmonary tuberculosis running a protracted course may be instances of pulmonary infection by some of the molds. (See Pseudotuberculosis, p. 375.)

LEPROSY.

Leprosy is a feebly contagious and highly malignant disease, due to the *bacillus lepræ*. (See p. 188.) The disease is probably propagated largely by inoculation in susceptible individuals, and manifests itself in two forms: (*1*) **anesthetic leprosy** and (2) **tubercular leprosy.**

1. **Anesthetic, smooth,** or **trophoneurotic leprosy** involves the nerves, skin, bones, and viscera. The nerves most commonly affected are the ulnar, median, radial, musculospiral, intercostohumeral, external cutaneous, posterior tibial, and peroneal. The nerve affected is red, swollen, and rounded in shape; later it

becomes harder, pale and grayish in color, with nodular or fusiform enlargements. Microscopically, the neurilemma may or may not be changed; in most cases, however, it becomes thickened, fibrous, and infiltrated with granule cells (leprous cells, lymphoid cells). Cicatrization and contraction may obliterate the function of the diseased nerve. The nerve lesion of leprosy begins as a perineuritis; the later degenerative changes are apparently due to the pressure upon the nerve and to interference with nutrition. Occasionally, the central nervous system shows some edema, and there may be an excess of fluid in the ventricles and in the subarachnoid space. The larger nerve-trunks are likely to show some fibroid hyperplasia, with slight atrophy; the cutaneous nerves are degenerated, hence the skin is anesthetic; the hair-bulbs, the sweat-glands, and the sebaceous glands are atrophied and fibroid. The eruptions of leprosy assume a number of forms. They are sometimes erythematous; sometimes attended by pigmentation, and at other times by reduction in the normal pigment. In purely anesthetic leprosy the maculæ are never elevated until late in the disease. As the result of the trophoneurotic disturbance, muscular contractures occur; these may be followed by, or associated with, a varying quantity of muscular atrophy. The fact that the patient feels no pain as a result of injury of the affected part tends to increase the danger from this source. The author has seen a case of leprosy in which the patient, a pipe-smoker, had burned off the ends of his fingers by pressing the tobacco down into his pipe. Necrosis and caries of the long bones have been observed.

2. Tubercular or Nodular Leprosy.—With infection of the skin or mucous membranes, preceded by the so-called prodromal eruptions, typical leprous tubercles are developed; "they may be flat or prominent, oblong or round, isolated or confluent, and in color varying from pale violet to dark brown; . . . . they are generally soft, but may be hard" (Danielssen and Boeck, quoted by Summer). These tubercles occur anywhere on the body, with the exception of the scalp; they are also rare in the palms of the hands and on the soles of the feet. Microscopically, each tubercle is made up of granulomatous tissue, composed of lymphoid and epithelioid cells retained in the loose connective-tissue matrix; in these masses the bacilli abound, both between and in the cells. Liquefaction necrosis occurs, followed by infection with pyogenic organisms, terminating in ulceration; such ulcers often heal rapidly, or, by extension, may lead to extensive sloughing; the nodules occur also on the mucous membranes, particularly that of the nose and larynx. The bacilli

may invade the viscera, lung, liver, spleen, and kidneys, in which they occasionally give rise to leprous nodules.

Mixed forms of leprosy are not uncommonly seen, both the anesthetic and the tubercular type being present. In other cases an attack of the anesthetic form terminates in the tubercular, or the tubercular type develops evidences of extensive anesthesia. It is held by many observers that the so-called mixed form is not truly a variety of leprosy, but is the ideal, complete, fully developed disease, and that the anesthetic and nodular types are incompletely developed forms. *Lepra mutilans* and the so-called *gangrenous leprosy* are inappropriate names intended to describe the conditions rather than the disease. Leprosy may be complicated by the occurrence of other processes; tuberculosis is frequent, and inflammations of the kidney, septicemia, pyemia, extensive intestinal ulceration, amyloid disease, etc., are frequent as associated lesions.

CHAPTER IX.

TEMPERATURE CHANGES.

INTOXICATIONS.—INFECTIONS.

The temperature of the human body remains practically constant, or about so, at 37° C. There are normally for each individual certain variations above or below the mean for the twenty-four hours; the maximum fall, in health, rarely exceeds 0.5° C., and is, for most persons, always at, or near, the same hour of the day; the same is true of the daily rise, so that between the daily maximum and minimum there is commonly about 1° C. of fluctuation. This daily curve of the temperature follows nearly the same course each day, so that the maximum is reached between 4 and 6 P. M., and the minimum between the same hours A. M.; this cycle for any given individual is nearly uniform, but no two persons are likely to have identical thermic curves. The following table, from Thoma, compiled by Jürgensen and Liebermeister, indicates the usual variations in body temperature at different hours in the day:

Time of Observation.	Temperature in the Rectum. (*Jürgensen.*)		Temperature in the Axilla. (*Liebermeister.*)	
	F.	*C.*	*F.*	*C.*
In the morning in bed,	(98°)	36.6°	(97.8°)	36.5°
Before breakfast,	(98.18°)	36.7°	(98°)	36.6°
After breakfast,	(98.36°)	36.8°	(98.7°)	37°
In the forenoon,	(98.8°)	37.1°	(99.18°)	37.3°
Before lunch,	(99.18°)	37.3°	(99°)	37.2°
After lunch,	(99.36°)	37.4°	(99.18°)	37.3°
In the afternoon,	(99.5°)	37.5°	(99.36°)	37.4°
Before dinner,	(99.7°)	37.6°	(99°)	37.2°
After dinner,	(99.36°)	37.4°	(98.8°)	37.1°
Before going to bed,	(98.8°)	37.1°	(98.36°)	36.8°
During the night,	(98.7°)	37°	(98°)	36.6°
	(98.36°)	36.8°	(97.18°)	36.2°
	(98.36°)	36.8°	(97.18°)	36.2°

The hypotheses and theories presumed to explain the mechanism of temperature regulation are based upon certain well-established facts. Heat, representing the cellular or tissue

activity, is generated within the body by the oxidation of food supplied or stored, or of the tissues themselves, is distributed largely by the blood, and is lost chiefly from the skin and respiratory mucous membrane. The regulation of the body temperature must be through means addressed to one of three agencies: heat production, distribution, or dissipation.

Heat production occurs in every organ and tissue, but the greatest thermogenic activity is manifested in the muscles, including the heart, and in the large glandular viscera: for example, the liver. The greatest heat production occurs in the voluntary muscles, including those of respiration. The heart muscle is presumed to afford a considerable supply of heat in the same manner as the other muscles, and, in addition, transmits force, which is indirectly converted into heat by the friction of blood against the cardiac walls and also against the walls of the arteries and capillaries, through the resistance of which the blood-pressure is largely maintained. The fact that the blood rises in temperature after passing through the liver is not surprising when the remarkable glandular activity of that organ is taken into consideration.

The distribution of the blood is largely controlled by the nerves supplied to the arterioles, and, as the dissipation of heat is largely dependent upon the distribution of the blood, the influence of vascular innervation upon heat loss is one of the most important elements to be estimated. Exactly what determines the action of the vasomotor nerves in the regulation of temperature is one of the unsolved problems in normal and morbid physiology. It would appear that there is somewhere a center, possibly more than one, that presides over the body temperature by regulating heat dissipation at least, if not its production, but probably both. The theory of heat regulation by the nerves implies a heat-regulating center (**thermotactic center**), with nerves controlling heat production (**thermogenic nerves**), nerves controlling heat dissipation (**thermolytic nerves**), and, possibly, nerves that influence heat-producing tissues in a way antagonistic to the thermogenic nerves (**thermo-inhibitory nerves**). This complicated system is assumed to have its center in the medulla; this center, acted upon by certain agents, manifests disturbance through the fibers of some of the nerves indicated. In addition to one center, or possibly more, in the brain or the medulla, there may be in the cord, or even in the larger ganglia, subsidiary centers influencing a region, or regions, only. While the theory of heat regulation through the nervous system may be considered to be far from demonstrated, the facts that no

attempt at heat regulation is made in animals possessing an indifferently evolved nervous system; that lesions of the higher evolved nervous system are followed by alterations in temperature regulation; and that the temperature, both normal and abnormal, may at times be influenced by hypnosis, would each seem to indicate relations between heat regulation and the nervous system that can not be ignored. The production of heat by the oxidation of food and of tissue elements, the distribution of the heat generated, and its final dissipation, are complicated phenomena that, with our existing knowledge, can be but imperfectly contemplated.

Hypothermia (Subnormal Temperature).—A temperature below the mean normal of the active period of life occurs in some forms of anemia, and in myxedema, chronic heart-disease, and cancer, follows shock and severe hemorrhage, is present in some forms of exhaustion or adynamia, and frequently follows marked elevations of temperature, particularly if prolonged; thus, after typhoid fever and pneumonia a period of subnormal temperature is often seen. Starvation or prolonged exposure to low temperatures, or the two combined, may give rise to a reduction in the body temperature. The explanation of this condition lies probably in the lessened heat production, although instances occur—as in the occasional cases of great cutaneous activity after hemorrhage and shock, and in cases of exposure to extremely low temperatures—in which more heat may be lost than normal; such a source for subnormal temperature, however, is rare. The reduction of temperature may also be caused by the circulation of certain poisons in the blood, as in diabetes, in which the temperature may sink 5° C. or even more. In this condition both heat production (thermogenesis) and heat dissipation (thermolysis) are probably at fault, the control and equalization of the two by the thermotactic power having been perverted by the influence of a noxious agent circulating in the blood.

Pyrexia.—Under certain conditions there arises a chain of phenomena which the clinician recognizes as *fever*. There is disturbance of a number of functions: appetite, secretion and excretion, the circulation, respiration, and, in many cases, the central nervous system, show marked disturbances. With one or more of these phenomena there occurs the one constant element of fever—*elevation of temperature* (**hyperthermia**). In moderate cases the temperature reached may not exceed 39° C.; in more severe cases it may reach 41° C., and in grave cases may go beyond 42° C. Temperatures exceeding 55° C. have been observed.

Causes.—Prolonged exposure of a warm-blooded animal to a temperature in excess of the normal temperature of the animal used for the experiment commonly induces hyperthermia. The rapidity of occurrence and the degree of hyperthermia are dependent upon the height of the temperature to which the animal is exposed, and are also apparently influenced by the medium through which the heat is applied. The temperature-rise is most marked if the animal is submerged in water; next in point of efficiency is air containing abundant moisture, while dry air is least efficient. Absence of moisture lessens the probability of the occurrence of hyperthermia, and individuals may be subjected to comparatively high temperatures in dry air and yet escape heat-stroke. In many of the industries laborers are exposed for a varying period of time to comparatively high temperatures; if such exposure be prolonged or if moisture be present, heat-stroke may ensue.

Hyperthermia may be produced by diseases or injuries of the central nervous system: puncture of the corpus striatum, lesions of the bulb, and destruction of the first cerebral convolution may be followed by hyperthermia. Hale White has recorded two cases of hemorrhage into the corpus striatum associated with a rise of temperature, most marked on the opposite side of the body, lasting in one case four days, and in the other, twelve days.

There can be no doubt that the most important causes acting in fever production are *bacteria and their products*. That the germs are not the essential element may be shown by the production of artificial temperature-rises by the injection of filtered and also of sterile cultures of certain bacteria into animals. The introduction of *preformed* poisons into the system gives rise to a chain of symptoms, the condition being termed an *intoxication*.

Microbic intoxications are not purely the outcome of laboratory experiment, but occur with regrettable frequency in practice. The symptoms of some of the infections are purely the evidence of intoxications: in diphtheria the bacillus may be limited, even in fatal cases to proliferation on the surface of the mucosa, many of the symptoms and all the lesions occurring elsewhere than at the point of growth, arising from the dissemination of the toxin through the lymphatics and its distribution eventually by the blood. A simpler example of pure intoxication, one frequently met is the infection of a blood-clot in the uterus following labor. The bacteria generating the poison in the blood-clot may never gain access to the living uterine tissues with less to the circulation, but the products of metabolism pass by absorption into the blood through the living and dead tissues.

they induce the phenomena of intoxication. A retained blood-clot between the flaps, in a recent amputation, becoming infected, acts in a similar manner. By reason of this danger, in addition to its mechanical interference with healing, surgeons recognize the necessity of avoiding "dead spaces" in which infection may be favored by lessening the protective influence of living tissues. Commonly, the organisms active in the production of bacterial intoxications are pathogenic in the true sense of the word. It is not to be forgotten, however, that bacteria normally unable to infiltrate living tissues, and hence properly classified with nonpathogenic organisms, may pullulate in dead tissue, and may elaborate poisons the absorption of which may give rise to grave intoxications. The intoxication arising from the absorption of microbic products is known as **septic intoxication,** or **sapremia,** and the element absorbed—the bacterial product—is termed **pyrogenous.** A peculiar fact, often observed, is that in the brain the products of bacterial life may not induce fever. This may be explained in a number of ways. Growing on different culture media, bacteria produce alkaloids with varying pyrogenous activity, and in the brain-tissues the activity or character of the microbic toxin, by reason of some peculiarity in the pabulum supplied, may be changed; the very fact that the abscess involves brain-tissue, and that the same may be potential in controlling temperature or in modifying it, may make the accident of location a determining factor in its influence on body temperature. Again, evidence is not wanting to show that dissemination of poisons is less rapid by absorption through brain-tissue, and this may in part explain the absence of fever in some cerebral abscesses; it fails, however, to offer any reason for the subnormal temperature at times observed.

The production of pyrogenous substances by animal parasites is well illustrated by the peculiar febrile phenomena of malaria. Experimental research into the exact nature of the fever-producing body elaborated by such organisms as the malarial parasite has not afforded any satisfactory conclusion, nor have we much to hope for in this direction until it becomes possible to study the parasite in artificial culture. It is commonly believed that during the segmentation of the protozoon there is elaborated a poison that brings about the rise in temperature. While such a view may be satisfactory, in a sense, we must not forget that the mere destruction of blood-cells may bring about fever, and when we recall that in malaria this process is particularly active, we can not ignore the possibility of its bearing something more than an associated relation with the fever present.

Intoxications arise, however, without the intervention of micro-organisms, either animal or vegetable. In cocain-, strychnin-, and brucin-poisoning, and following the introduction into the circulation of certain animal poisons, as from snake-bites, stings of scorpions, etc., typical intoxications occur. Not in all of these is there elevation of temperature.

In addition to the toxic bodies introduced from without,—such as those just mentioned, and among which may be included mussel-poisoning,—intoxications may arise from poison generated within the body—**auto-intoxications.** The latter include **enterosepsis,** or **copremia,** an intoxication occurring from the retention of intestinal contents, as in chronic constipation. The toxic material here is not wholly a microbic product, nor is it entirely the result of retention and absorption of noxious agents of purely animal origin, but is composed of a mixture of the two causative factors.

There is another source of fever-producing or pyrogenous material in tissue dissolution and in the formation of certain exudates; the exudates thrown out in the process of repair, during the formation of blood-clots,—as around fractured bones and under similar conditions,—contain some agent that, by absorption, produces elevation of temperature. The chemistry and even the identity of the body is still a matter for speculation. Brieger noted the constancy of fever and fibrin formation, and surmised that the cause of both was the ferment presumed to cause the separation of the liquor sanguinis into fibrin and serum; this view meets with general acceptation. The rise of temperature that follows a surgical operation, the fracture of a bone, or an interstitial hemorrhage is presumed to be due to this ferment—a pyrogenous material generated during the breaking up of certain tissues of the body, commonly blood. These fevers—**surgical aseptic fevers**—are not usually classed with the intoxications, as they do not arise from the introduction from without of preformed poisons, but in some points their resemblance to copremia permits of their mention with the intoxications, as illustrative of certain causes operative in the production of fever.

Local Infections.—In sapremia the poisons generated by the bacteria are elaborated outside of living tissues, and in septicemia the poisons are generated by the bacteria in the blood. Intermediate between these are the local tissue infections, in which the bacteria invade living tissue, from which the microbic poisons are absorbed into the circulation, either directly, through the capillary walls, or indirectly, by the lymphatics. In diphtheria the bacteria may be residents on the surface of the mucosa only, the toxins

disseminating beyond and inducing necrosis,—more dead tissue, —into which the bacteria grow. In some cases, however, the bacteria pass the dead membrane and infiltrate the living tissues; there is then a local infection of living tissues as well as a growth in the dead, or necrotic, adjacent structures. Erysipelas, abscess formation, the initial lesion of anthrax, and, under similar conditions, many infections, are in part—primarily, at least—but local infections, with dissemination or absorption of the microbic products giving rise to the phenomena of an intoxication, the blood escaping actual invasion by the bacteria. The local infections, with the systemic symptoms due to the absorption of toxins produced in the living tissues, stand intermediate between pure intoxications, such as sapremia, and the mycoses of the blood.

Any infection, whether localized or widely diffused, may be **simple**: that is, *single*, or due to but one germ, as a pure or simple infection by the streptococcus of erysipelas. A simple or single infection may be followed by the introduction of a second germ; the additional infection is known as a **secondary infection.** As an example of the last-named infection, we have the infection of a tuberculous area with an organism of suppuration. A secondary infection may be followed by a **tertiary infection,** and so on. Again, we may have a number of infections occurring, so far as we can determine, at one time; the process is then said to be a **mixed infection.** It is interesting to note that in the mixed and secondary infections it is not necessary that all of the bacteria present should belong to the pathogenic class. If one of the microbes be disease-producing and lead to tissue necrosis, the secondary infection may be by a saprophyte living upon the dead tissue resulting from the necrotic processes induced by the pathogenic organism. As a rule, mixed and secondary infections are more grave than simple infections, because the additional ferments produced by the second germ can but intensify the dangers to which the patient is subjected. While of little practical importance, the fact remains demonstrated that certain bacteria are antagonistic to each other, and that two organisms can be selected in the laboratory that, if simultaneously introduced into an animal, will not prove fatal as quickly as one of them alone. This fact is not, in the present state of our knowledge, explicable, and is of theoretic interest only, as the conditions probably never occur except in experiment.

The fact that nonpathogenic bacteria live and produce noxious elements in the necrotic tissues produced by pathogenic bacteria leads us to see how dead tissue, or tissue with its protective

powers in a state of abeyance, as after extensive bruising or laceration, may permit the growth of bacteria that, in less injured tissues or in healthy structures, would immediately succumb to the protective powers of the animal. For these reasons injured structures and tissues with greatly reduced nutrition may need a protection from infection not demanded by healthy tissues.

Mycoses of the Blood.—In these the bacteria are present and multiplying in the circulating blood, in which their products are generated. The intensity of the septic phenomena is augmented by the greater production of the poison, and, not having even the barrier of protection afforded by the necessity of osmosis or absorption, they are enabled to engender lesions not presumed to occur—at least, not to the same extent—in either sapremia or local infection. The term **septicemia** was meant to cover, probably, some local infections, as well as mycotic invasion of the blood, but particularly infection of the blood by the organisms of suppuration. That the common pyogenic bacteria are not the exclusive source of septicemia is shown by the reported instances of clinically typical cases of the disease, without the presence of the pyogenic cocci, but resulting from the action of other bacteria, as the diplococcus of pneumonia, bacillus typhosus, colon bacillus, bacillus pyocyaneus, and other organisms. The organisms not only proliferate in the blood, but also, in occasional cases, are found growing by implantation (*mural implantation*) on the walls of some part of the circulatory system, as the valves of the heart in ulcerative or malignant endocarditis. This implantation on the walls of the blood-vessels, heart, sinuses, etc., may lead to the development of thrombi; and from these, emboli; or, possibly, massing of elements in the blood may lead to emboli—emboli formed in transit. The last is a questionable hypothesis. The emboli formed in blood, and containing bacteria, are, of course, septic, and at their point of lodgment engender the changes already considered when discussing embolism. The embolic production of abscess is the essential element of **pyemia**, a disease recognized by surgeons as septicemia plus the infected emboli to which are attributed metastatic abscesses. (See Thrombosis and Embolism, pp. 267 and 275.)

The fever that accompanies the septic processes is peculiar, on account of the remarkable exacerbations, which usually occur daily; and, in the graver forms, on account of the addition of repeated **rigors** or **chills**. Rigors are not restricted to septic processes, but occur also after hemorrhage, occasionally after shock, and as a poorly understood purely nervous manifestation;

they constitute the most marked phenomenon of the malarial paroxysm.

During the cold stage, or chill, there is a determination of the blood to the large glandular viscera and venous trunks; the skin is thus deprived of its normal heat by the deficiency of its blood supply, and the cooling of the cutaneous nerves affords the explanation for the patient's sense of intense chilliness. That the low temperature is purely a cutaneous phenomenon is shown by the thermometer. If the temperature be taken in such a way as to estimate the actual blood-heat,—as in the rectum, mouth, or axilla,—preventing heat dissipation at the point at which the temperature is being taken, we find the temperature to be above the normal. The deficiency of the cutaneous circulation lessens heat dissipation, and probably at the same time heat production is increased. Certainly, in some fevers there is an increase of heat production, as abundant evidence is not wanting to show that heat dissipation may be greater than normal, and yet that elevation of temperature may persist—a condition impossible without persistent overproduction. The rigors associated with reduction of surface temperature due to the exposure of the body to a medium the temperature of which is low, appear to be reflex phenomena, brought about by an attempt on the part of the economy to produce more heat in response to the recognized surface fall. They are to a certain extent under the control of the will. The amount of temperature reduction necessary to the production of a rigor is usually not over from 0.5° to 1° C. It is interesting to observe that in pyrexia a chill results whenever the surface temperature is from 0.5° to 1° C. lower than the internal temperature. After persisting a varying length of time, the chill ends by a return of the blood to the skin, and usually rapid heat dissipation, though by no means always, followed by a marked decline in body temperature.

The *acme* or *fastigium* of the fever may be quickly reached; its duration may be brief, or, in other cases, the fever may persist at about the same point for a considerable length of time, usually showing slight matinal and vesper oscillation. The fever may disappear within a few hours (*crisis*) or may gradually subside, requiring as many days (*lysis*).

Whether preceded by a chill or not, the acme of the temperature-rise is commonly followed by a progressive decline, associated with hyperactivity of the emunctories, particularly the skin. This gradual decline usually begins in the afternoon or early evening and progresses through the night, with the early morning temperature the lowest, the rise beginning at this time and reaching

its height during the afternoon. During the twenty-four hours fever may disappear, only to reappear in a few hours; this type is said to be *intermittent.* In the *remittent type* there is more or less marked remission, but no period of complete apyrexia.

The causes active in producing this rhythmic alteration in temperature are obscure. It is maintained that the accumulation of pyrogenous material, and its tendency toward fever production in the system, is at first compensated for by the thermotactic powers; eventually, the failure to excrete the poison as rapidly as produced permits of such excessive accumulation that the heat-regulating forces are inadequate to the task of maintaining a constant temperature. This is followed by a rise, which continues until the exhausted centers, which normally responded to slight temperature variations by adjustment of the mechanism between heat production and heat dissipation, respond to the more urgent demand for heat dissipation by a pseudocrisis, during which the temperature falls. The depressed or exhausted center, not responding to the slight changes that would affect it in health, now permits another accumulation of heat, which again sets it off, the process being repeated day after day as long as the pyrogenous material is thrown into the circulation.

Paradoxic Pyrexia.—None of the hypotheses at present available explains satisfactorily the occurrence of what Dr. Savage has called "mad calorific areas." Such a condition is illustrated by a case reported by Knowling, in which at one time the temperature was 99.4° F. in the left axilla and 105° F. in the right. An explanation that at once suggests itself is that vascular dilatation on one side of the body or in a certain area permits ready access of the blood coming from the viscera, resulting in higher temperature, while a less active peripheral circulation in other parts of the body to a certain extent conceals the internal hyperthermia. Often there is no evidence of such vascular dilatation, and in the absence of phenomena that would favor this conclusion it would probably be wrong to accept it as final.

It has been held that thermolysis may be increased upon the opposite side, and hence the temperature-rise is marked upon the side in which thermolytic activity is diminished. With regard to this theory and to the opinion previously given, we can only say that both are speculative, and that neither rests upon a basis of fact that would justify us in formulating a definite opinion at this time.

With the rise in temperature certain circulatory phenomena manifest themselves. Thus, for every degree Fahrenheit (0.55°

C.) that the body temperature rises, the pulse-rate is increased ten beats. This observation is approximately correct for temperature-rises within two or three degrees, but with higher temperatures a greater rise occurs; Liebermeister showed that, for the 1° C. above 41° C., the number of heart-beats increased 27.

During the earlier stages of fever the *blood-pressure* is likely to rise also, but the early relaxation of the vasomotor nerves—probably due to exhaustion, degenerative changes, or inefficient nutrition—is followed by a reduction of blood-pressure. More important than the disturbance of blood-pressure, although no doubt largely due to the same, is the *change in the blood distribution;* in fever the latter often varies greatly, as already stated when considering the dissipation of the abnormal heat. The large glandular viscera are not infrequently perceptibly altered by the increased amount of blood sent to them, and by its relative, if not absolute, stagnation in their interior.

Blood Changes.—The blood is materially lessened in nutritive value, partly as a result of the interference with assimilation, both primary and secondary, and partly from the destruction of the blood elements. The hematolysis is not usually manifest until the fever subsides, not having been marked previously by reason of the concentration of the blood, so that a blood examination during the height of the fever fails to disclose the loss of globular elements until, by dilution, after the fever has disappeared, the oligocythemia and oligochromemia become apparent.

Changes in Organs.—In considering alterations that occur in the tissues we are at once confronted with the difficult task of differentiating lesions that are due to the febrile process alone from lesions that are dependent upon the action of poisonous agents—such as toxins, etc.—that were themselves etiologic factors in the production of the fever. It is not improbable that many of the tissue alterations attributed to the rise in temperature alone are truly dependent upon the action of the poisons that brought about the fever. In addition to the changes in the blood, other tissues show marked alteration. The large glandular viscera, particularly the liver and kidneys, exhibit cloudy swelling; a similar change occurs in the muscles, the heart often manifesting the granular alteration of its fibers to the highest degree. Hyaline change in the muscles has also been observed. The adipose tissues sooner or later show wasting, and the nerve elements evince the granular and pigment alterations incident to exhaustion. The mucous membranes, that of the alimentary canal in particular, present granular and fatty changes. Many of the tissue changes may arise from contact

with the poisons circulating in the blood; others are possibly due to the accompanying elevation of temperature and to associated disturbances of nutrition.

Experimental evidence has seemed to demonstrate that a rise in the body temperature may be, in certain infections, distinctly beneficial. In pneumococcous infection it has been found that resistance is increased by maintaining the animal at a temperature between 41° and 41.5° C. Similar results have been obtained with the streptococcus of erysipelas and with a few other organisms. Should further research establish the correctness of these experiments, it is not impossible that we may have to revise, indeed reverse, our views as to the essential etiologic factors active in fever production. Thus, it may be shown that leukolysis and the liberation within the body-fluids of antimicrobic bodies belong to the protective phenomena, and that these bodies can bring about the elevation of temperature, which is itself a part of the protective process. Investigations directed along this line may show that the temperature-rise accompanying the malarial paroxysm may be the cause of sporulation, and that the latter is not the cause of fever, as some at present hold. In the present state of our knowledge such suggestions can scarcely be dignified by calling them even hypotheses; the fact that fever accompanies infection—indeed, seems to be its most constant companion—demands a better explanation than is at present available.

PART III.

SPECIAL PATHOLOGY.

PART III.—SPECIAL PATHOLOGY.

CHAPTER I.

THE BLOOD.

TECHNIC OF BLOOD EXAMINATION.

Examination of the Blood.—Blood is examined microscopically to determine the number and character of the corpuscles and their relative proportion, and the presence or absence of microorganisms and parasites. Estimation of the hemoglobin is also of the greatest importance. Blood should always be examined in the fresh, unstained condition, and this should be followed by a study of stained specimens.

To obtain the blood, cleanse carefully the lower part of the lobe of the ear, using, first, soap and water, followed by water, alcohol, and ether, in the order given, and rubbing the ear vigorously to induce hyperemia. The ear and the finger-tip, because of their accessibility, are the points usually selected for drawing the blood; other areas may be equally available. The region chosen should be free from edema, inflammation, or any other morbid process likely to give rise to the presence of other fluids that may become mixed with the flowing blood. With a lance-shaped needle prick the skin quickly and to a good depth. The author is averse to the continuous use of a single instrument, and therefore hesitates to recommend any of the many devices for pricking the skin. There is no reason for the repeated use of the same instrument. A pen, preferably of steel, with one nib broken off, as recommended by a number of observers, is cleanly and inexpensive, enabling one to use a different pen for each observation. Let the first few drops escape and wipe them off, using for examination only the blood that follows. Have at hand at least a dozen cover-glasses, carefully cleaned in acid alcohol followed by alcohol and careful wiping; four slides cleaned in the same way should be at hand. A square cover-glass, gently warmed, not hot, is allowed to touch the drop of blood; a droplet adheres, and the

cover-glass is inverted, drop downward, on a warm, clean slide. As soon as the blood runs to the edge of the cover-glass, with a sable brush, cedar oil—conveniently obtained from the immersion oil that accompanies the microscope—or vaselin is painted around the edge to exclude air and to prevent drying. The slide is now ready for examination. A second and a third slide are prepared in the same manner. A very satisfactory method for obtaining slides, with minimal exposure of the blood to the air, is to take a thoroughly clean slide and cover-glass, so adjusting them that the cover on top of the slide comes even with the edge; when the edge is presented to the drop of blood, barely touching it, the blood flows, by capillary action, between the two glasses. Slides so prepared can not be so readily sealed, but when the space between the cover-glass and the slide is completely filled, drying of the serum at the margin more or less perfectly excludes the air. Such temporary mounts will not keep, and must be examined at once, using first low powers and then higher. While the blood is flowing another cover-glass is touched to the drop, so that the center of the glass receives the droplet; immediately, a second cover-glass is dropped on the first, care being taken that the corners do not coincide; if the glasses are clean, the blood quickly flows to the edge; at once separate the two covers by sliding them apart, carefully avoiding any lifting motion; dry quickly, but avoid heating while moist. At least eight or ten spreads should be prepared in this way from each case. These must now be fixed.

Fixation of Films.—The best method for fixing is by heat, as in a hot-air oven or sterilizer at 125° to 140° C. for about twenty minutes. The lower temperature requires a longer time. Ordinarily, satisfactory results will be obtained if the temperature be slowly raised to between 125° and 130° C., the heat withdrawn, and the oven permitted to cool slowly. Ovens constructed on the principle illustrated in figures 49 and 50, page 81, are best adapted for the fixation of films. In the absence of an oven a copper plate or strip is convenient; a strip from 5 to 10 cm. wide and from 20 to 30 cm. long, supported over a flame and protected from drafts of air, answers very well. The flat-iron-shaped table (Fig. 25, p. 51) may be used in the same way. Being at one end, the flame soon heats the strip so that at any point a fairly constant temperature is maintained. By dropping water on this plate at various points a place is found where water boils; drop the cover-glass on this point, turning the film side down; about twenty minutes will be needed for fixing. A number of competent observers fix the dried films as already directed for

the fixation of films for bacterial staining. (See p. 94.) For a finer study of the nuclei in blood-cells, and when a study of the granules is not so important, some of the fixatives recommended in chapter II may be used; solutions containing bichlorid of mercury, and also the osmic acid solutions, may find special application. (See p. 48.) Cover-glass films may be fixed by immersion in a mixture of equal parts of absolute alcohol and ether for half an hour, followed by drying. After fixation by any of the foregoing methods the covers may be stained at leisure.

Staining.—Properly prepared and fixed films are grasped in the cover-glass forceps (Fig. 64, p. 95), as already directed for staining bacteria. The stain may be applied to the cover, as shown in figure 63, page 93, or the cover, grasped in Kalteyer's forceps, may be immersed in a dish containing the stain, as shown in figure 64, page 95.

Stains.—A mixed powder for the preparation of Ehrlich's stain is on the market, and was recommended in the previous edition of this book. Extended experience has led the author to believe that solutions prepared from the mixed dry stain are rarely satisfactory, and for this reason it is recommended that the stain be made from concentrated aqueous solutions of the dye. The solutions are all to be saturated, and the quantities given will insure saturation from almost all samples, but as the dyes vary in solubility, different samples may require slightly more or less of the dye. As it is best not to filter, and as only the supernatant fluid is to be used, it will be found convenient to make up all these stains in tall, narrow bottles, and, while more expensive, Grübler's stains had best be used.

1. Saturated aqueous solution of orange G:

Orange G,	6 gm.
Distilled water,	100 c.c.

2. Saturated aqueous solution of acid fuchsin:

Acid fuchsin (fuchsin S),	9 gm.
Distilled water,	100 c.c.

3. Saturated aqueous solution of methyl-green:

Methylene-green (oo cryst.)	6 gm.
Distilled water,	100 c.c.

These stock solutions keep well. The mixed stain prepared from them has not such good keeping qualities, and, while not ripe for the best results under one week, after two or three weeks usually does not stain so well; occasionally, however, a sample

may give fairly good results for months. A little experience enables one to see which of the three stains is deficient, and by adding a trace of the required stain, the mixture can be improved. Hardly any two blood cases stain alike, and, for the best results, slight changes in the formula may be made in order to overcome this defect. Ehrlich's formula, as given by Cabot, and the Johns Hopkins formula, as given by Simon, are as follows, made from the foregoing stock solutions:

	Ehrlich's Formula.	*Johns Hopkins Formula.*
(*a*) No. 1,	120 to 125 c.c.	18 c.c.
(*b*) No. 2,	80 to 165 c.c.	9 c.c.
(*c*) No. 3,	125 c.c.	20 c.c.
(*d*) Glycerin,	100 c.c.	5 c.c.
(*e*) Absolute alcohol,	200 c.c. (alcohol, 94%)	15 c.c.
(*f*) Distilled water,	300 c.c.	30 c.c.

In the preparation of the stain it is important that a definite order be followed in the mixing of the foregoing ingredients: that is to say, *a* should be measured, then *b* should be measured and slowly added to *a*, with constant agitation; to this *c* should be added in like manner, and so on throughout the list. Stain the fixed films for from two to five minutes, wash in distilled water, dry, and mount in balsam.

Canthack and Hardy especially recommend a 0.5 per cent. solution of eosin in seventy per cent. alcohol; stain for thirty seconds, rinse in water, dry by gentle pressure between folds of filter-paper, pass three times through the flame, and counterstain in Löffler's methylene-blue solution. (See p. 67.) At present there is a decided tendency to use dyes separately. For the demonstration of structurally imperfect red cells a one per cent. solution of eosin (water soluble) in fifty per cent. alcohol, followed by washing in water and then by hematoxylin, gives satisfactory results.

To stain the basophilic "mast cell" use:

Saturated alcoholic solution of dahlia, filtered,	50	parts.
Glacial acetic acid,	10–15	"
Distilled water,	100	"

Stain for twenty-four hours, wash in water, dry, and mount in balsam. Satisfactory stains of this cell may be obtained by the use of carbol-toluidin-blue (p. 67) applied for a few minutes, followed by differentiation in glycerin ether (p. 68); the granules are more sharply outlined by this method, and the results are more uniform.

Staining Diabetic Blood.—Bremer's observations on the

peculiar stain reactions of diabetic blood appear to deserve much more consideration than they have received. From a number of experiments in the author's laboratory he is convinced that certain information may be obtained by Bremer's methods, and that the test is deserving of consideration. It requires constant control under nearly all conditions, and hence every examination must be controlled by applying the test to blood known to be normal as well as to the suspected specimen. Films of the blood under examination and control films, both prepared in the usual way, are fixed by heat at a temperature of 135° C. The two covers are then grasped back to back, so that both films are exposed, and are immersed in either a one per cent. watery solution of Congo red or a one per cent. watery solution of Biebrich scarlet for about two minutes. The films are then washed in water and dried. Congo red stains the normal blood and not the diabetic; Biebrich scarlet stains the diabetic blood and not the normal. Other anilin dyes may be applied in a similar manner. The important point to be recognized is that diabetic blood is never stained to the same degree, and often not the same shade, as the normal blood.

ESTIMATION OF THE HEMOGLOBIN.

Gowers' Hemoglobinometer.—This apparatus consists of two glass tubes of exactly the same size; one contains a standard solution, the tint of a dilution of 20 c.mm. of blood in 2 c.c. of water (1 : 100).* The second is graduated into 100 degrees, and is arranged to contain 2 c.c. (a hundred times 20 c.mm.), or more, when the percentage of hemoglobin is above 100.

Twenty cubic millimeters of blood are measured by the capillary pipet and ejected into the bottom of the graduated tube, a few drops of distilled water being first placed in the latter. The mixture is rapidly agitated by a rinsing movement, and distilled water is then added, drop by drop, until the tint of the dilution is the same as that of the standardized tube. The degree of dilution indicates the amount of hemoglobin, and may be read off from the graduated tube.

Von Fleischl's Hemoglobinometer.—The standard of comparison in this instrument is an elongated wedge of glass, tinted with Cassius' golden purple, and mounted movably beneath a platform or stage like that of a dissecting microscope. In the

* In reality this represents a dilution of 1 : 101, but, as allowance is made in the graduated tube for this error, it is a matter of no real importance.

center of the platform is a circular opening, through which the light from a candle or lamp is reflected upward from a disc of plaster-of-Paris.

The wedge of glass underlies one-half of the circular opening in the platform. Above the wedge, and exactly over the circular opening, rests a metallic tube, 1.5 cm. long, with a vertical metallic partition and a glass bottom. One-half of the tube overlies the wedge and receives its light through it. This half is filled with distilled water, and in the other half is placed the mixture of blood and water. The blood is received from the finger into a minute glass tube by capillary attraction (automatic pipet) and is placed in the proper compartment, thoroughly mixed with

FIG. 229.—GOWERS' HEMOGLOBINOMETER, IMPROVED FORM.

A and *B* are two flattened tubes, *A* being permanently sealed and containing the tint standard; *B* is graduated, and is used for diluting the blood. *C* is a pipet for measuring the blood, as directed in the text. Just in front of the case is shown the needle usually recommended for puncturing the skin. The dropping-bottle shown in the illustration contains distilled water for diluting the blood.

water,—care being taken to see that the measuring tube is washed free from blood,—and both compartments are filled with water. In order to make accurate readings the observations must be made in a dark room or closet, using no other illumination than that afforded by a lamp or candle. The red glass wedge is then moved in one direction or the reverse until the two fluids show an equal intensity of red color. The number indicated on the scale, read off at *M* (see Fig. 230), is the percentage of hemoglobin. As soon as the automatic capillary pipet is emptied into the chamber *a* and rinsed free of the adhering blood, it should be placed in water or in a one per cent. solution of carbonate of

sodium, and should never be permitted to dry until it has been thoroughly cleansed. Immediately after completing the observation the mixing cell *G* is thoroughly washed and dried; the capillary pipet is also cleansed by repeated washing in the sodium solution, followed by water, or in water alone. It is then dried by passing a thread of cotton, silk, or floss through the capillary tube; a threaded needle is sometimes advised for this purpose, but chipping of the wall of the tube may result from slight carelessness in introducing the needle, and a hair doubled on itself answers the same purpose without the danger indicated. The

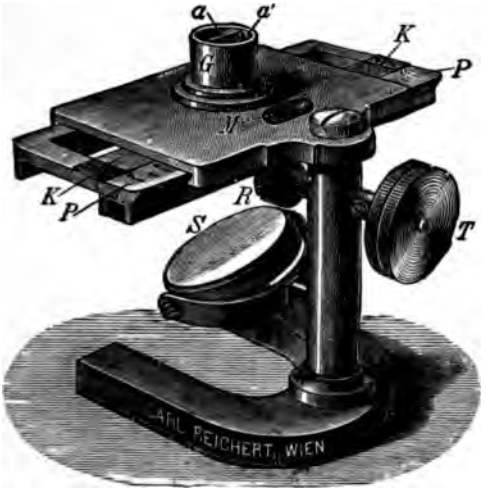


FIG. 230.—VON FLEISCHL'S HEMOGLOBINOMETER.

G. Mixing cell, divided by a partition into two chambers, *a* and *a'*. The blood and water are placed in *a*; *a'* receives water alone, and is directly over the colored glass wedge. *K, K*. Glass wedge. *M*. Point at which reading is taken. *T*. Milled head, which moves the head *R*, which, in turn, moves the carriage *P, P*, carrying the tinted glass wedge. *S*. Disc of plaster-of-Paris for reflecting the light upward through the glass wedge and the mixing chamber.

two ends of the hair are passed through the tube, and the resulting loop is used as a carrier for the thread, which completes the cleaning and drying. The beginner should see that the instrument is clean before the various parts are put away; the experienced worker is fully aware of the difficulty often encountered in cleaning a dried pipet, and therefore does not need the precautionary advice given to the novice.

The mixing pipet of each instrument is adapted to *that instrument only*, and bears its capacity stamped upon the handle. A similar marking is made on the screw-head at the back of the

stage, and as all parts of the instrument are, or should be, numbered; mixing of different pieces should not occur. In order to avoid confusion or incorrect reading where a number of instruments are in use, and when ordering new pipets, this fact must be remembered.

Oliver's hemoglobinometer consists of: (1) An automatic blood pipet (Fig. 231, *c*); (2) a mixing pipet (Fig. 231, *d*); (3) the blood-cell and cover-glass (Fig. 231, *c*); (4) the sets of standard gradations (Fig. 231, *a*); (5) the riders; (6) the camera tube; (7) the light; (8) a bottle of antiseptic fluid, the lancet, and needles and thread.

1. The automatic blood pipet (Fig. 231 *c*) has a capacity of five cubic millimeters and fills readily by capillary attraction. It differs from the fragile capillary measurer that accompanies von Fleischl's instrument in being made of stout glass, and is, therefore, more serviceable; in being larger and more easily manipulated; and in having the end that is presented to the blood well polished, so that all traces of blood can be removed from it by the finger. The bore is dried out before an observation by passing through it a needle, threaded with darning cotton. The handle is useful for stirring together the blood and water in the blood-cell.

2. The mixing pipet is provided with a rubber nozle that fits over the polished end of the blood-measurer and insures the complete rinsing out of the blood with the first few drops of water.

3. The blood-cell is of a capacity more than sufficient to insure the complete liberation of the hemoglobin. It yields a blood solution of rather less than one per cent. when filled level with the rim. It is itself the measure of the amount of water to be added, and may be easily and accurately filled.

4. The standard gradations are arranged as circular discs in two slabs—six in each; they represent the divisions of ten degrees of the scale from 10 to 120 inclusive.

5. The riders are small squares of tinted glass provided for the reading of the degrees intervening between each of the standard gradations. When they are used, the slip of colorless glass is placed over the cover of the blood-cell, so as to balance the effect of the layer of glass in the rider, which is laid over the standard. Two sets of riders have been arranged: one suitable for physiologic observation, to insure the finer readings,—*e. g.*, of one degree,—and the other, sufficient for ordinary clinical observation, to enable the observer to determine differences of 2.5 degrees. For the reading of units, nine riders are

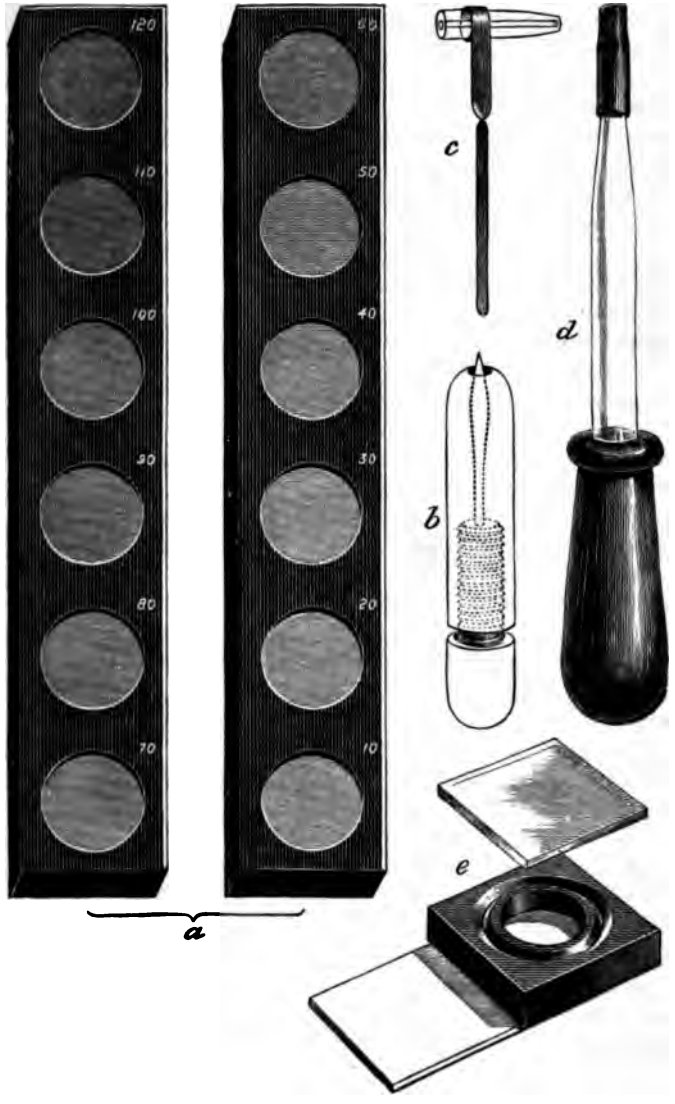


FIG. 231.—OLIVER'S HEMOGLOBINOMETER.
a. Standard gradations. *b*. Lancet. *c*. Capillary measuring pipet. *d*. Mixing pipet. *e*. Blood-cell and cover-glass.

required, which are grouped into three slides. It should be premised that the value of the riders is the same neither in the two standards required for candle-light and daylight nor in the upper and lower halves of either standard. This want of uniformity arises from the differences of the specific color-curves in the two standards, and in the two portions of each. In the six lower grades of both standards the value of each rider is double that in the upper six gradations. In the transition grades—the lowermost of the upper half and the uppermost of the lower half—this rule does not accurately apply, but inasmuch as the departure is constant in all observations, and is, moreover, slight, it may be disregarded for the sake of simplicity in using the riders.

The daylight standard is less adapted to the finer readings than the candle-light one, because the value of each rider, when used with it, is doubled: *i. e.*, No. 1 rider becoming equal to two degrees in the upper half of the scale and to four degrees in the lower half; therefore the candle-light standard is preferable for such readings; and when it is used, each rider has an equivalent value in the six stronger grades (first degree) and a double value in the six weaker grades (second degrees).

For the ordinary reading one rider is used: namely, that which is equivalent to five degrees in each slab of the standards. Therefore each set of six standard gradations, whether for candle-light or daylight, has its own rider. When the blood solution is deeper in color than any particular standard gradation, but is overstepped by the rider, the mean between the two may be taken as the reading; and the same rule will apply when the color of the blood is higher than the rider, but is not so high as that of the next standard grade above. Hence, this single rider may be made to provide readings of 0.25 and 0.75.

6. The camera tube: A tube of simple construction is provided, which, being collapsible, will pack into a small compass with the other parts of the apparatus.

7. The light: For observation by artificial light it has been found that the small-sized wax candles known as Christmas candles are the most satisfactory in affording a suitable intensity of light, and a light, moreover, that is sufficiently uniform.

The position of the candle is important. It should be such as to shed an equal light on the blood-cell and the standard, and also such as to furnish a high light, so that the flame should be three or four inches above the cells. The distance must be regulated by the observer, who will soon learn how to adjust it to the best advantage, so that he may watch the colors with the greatest certainty and accuracy. The actual distance does not

affect the reading; but when the candle is placed too near the points of observation, the illumination becomes too strong, and is somewhat distracting, especially when the lower grades are under observation, these requiring less light.

In daylight all colorimetric modes of estimating hemoglobin are more or less unsatisfactory, for they require a uniform degree and kind of light that can not always be obtained when daylight is resorted to. The color of the blood solution varies in a marked degree according as the light is blue or white, or is feeble or wavering, or is strong. Therefore, the candle-light standards are to be preferred, as being always available with a uniform light.

8. The antiseptic fluid and pricker: Before every observation the pricker should be dipped into an antiseptic solution that will not corrode the metal, and a little of the solution should be smeared over the part to be pricked. A mixture of equal parts of carbolic acid and spirits of wine is to be preferred.

To Use the Instrument.—The bore of the blood-measurer is first of all dried out by passing through it a needle threaded with darning cotton, and then the polished point is presented to the drop of flowing blood, obtained as directed for other instruments (p. 397). Care must be taken that the pipet is really quite filled; and if it has been necessary to reapply it to the drop, it should be observed whether there is a break in the column of blood. Any blood adhering to either end must be carefully wiped away with the finger. The rubber nozle of the mixing pipet, charged with water, is adjusted over the polished end of the measuring pipet, and the blood is washed into the blood-cell by pressing the water through, drop by drop. The handle of the pipet is then used as a stirrer, and the further additions of water are made to impinge on it, as it serves to graduate the size of the drops required accurately to fill the cell. It is easy to do this when the observer catches the reflection of a window on the surface of the fluid. A final thorough mixing with the handle will be required, and perhaps another slight addition of water may be necessary to secure a level filling. The cover-glass is then adjusted, when a small bubble should form—a sure sign that the cell has not been overfilled. If candle-light is to be used, the instrument must be removed to a darkened room, as already directed for von Fleischl's instrument (p. 402). The blood-cell is then placed by the side of the standard gradations, and the eye quickly recognizes its approximate position on the scale. Then the camera tube will more accurately define it. If it is found that the blood solution is matched in depth of color by one of the standard

grades, the observation is at an end; but if it is observed to be higher than one gradation, but lower than that above it, the blood-cell is placed opposite to the former, and the riders are added to complete the estimation.

In all tintometric observations take a standard time for looking down the camera tube. The trained color-measurers at Mr. Lovibond's color laboratories at Salisbury find that a ten-second observation is most convenient. When the eyes are shielded from light, their power of color-appreciation rapidly changes; therefore, after looking for ten seconds down the tube provided, if the observer is not satisfied as to the matching or otherwise, the head should be raised for a moment, to fill the eyes, as it were, with the general light, whether candle-light or daylight.

If the eyes are at all strained with long working, it is well to look for a moment on the inside of the lid of the instrument case, which is lined with green morocco, complimentary in color to the blood and the color-standards. This very rapidly restores the acuteness of observation. After completing the observation the same care is requisite in cleaning the instrument as already advised when considering the von Fleischl hemometer.

Dare's Hemoglobinometer.*—In this instrument the undiluted blood, in a very thin layer, is compared with a glass color-comparison prism. The principle involved is in some respects like that operative in the von Fleischl instrument, but differs in the fact that pure blood is used. The accompanying illustrations (Figs. 232 and 233) explain the different parts of the instrument.

To Make the Observation.—Before drawing the blood the instrument should be prepared for immediate observation by swinging the screen (T, Fig. 232) outward and attaching the camera tube (U, Fig. 232) and candle-holder (Y, Fig. 232). The candle should be pressed into the holder at such a level that the wax at the wick-end will be on a level with the top of the spring clamp that holds the candle; any curve in the candle-

* This very ingenious instrument has been devised by Dr. Arthur Dare in the Outpatient Medical Department of the Jefferson Medical College Hospital. Personally, the author has never used the instrument, although Dr. Dare has been kind enough to demonstrate its construction and method of use to him. Dr. Dare has made over five hundred comparative tests with the instruments of Oliver and von Fleischl, and has found that it gave readings always close to those of Oliver's instrument, but commonly showed different results from the von Fleischl hemometer, more especially in the high and low percentages. As these are the weak fields for the last-named instrument, and as Dr. Dare's device does not seem open to the same objections, it seems reasonable to suppose that it may supersede the hemometer of von Fleischl. No printed description of Dr. Dare's instrument has appeared, nor has he given it a name; the author has, therefore, ventured to call it Dare's hemoglobinometer. The instrument will be less expensive than the von Fleischl hemometer.

wick should be so turned that its convexity faces the instrument, and the flame should be in line with the metal shank in which the spring clamps are attached, so that the intensity of the candle-light will be equally divided on both the blood and color-comparison sides. As the comparison should be made as soon as possible after the blood has been drawn, a means of lighting the candle should also be at hand. The pipet for

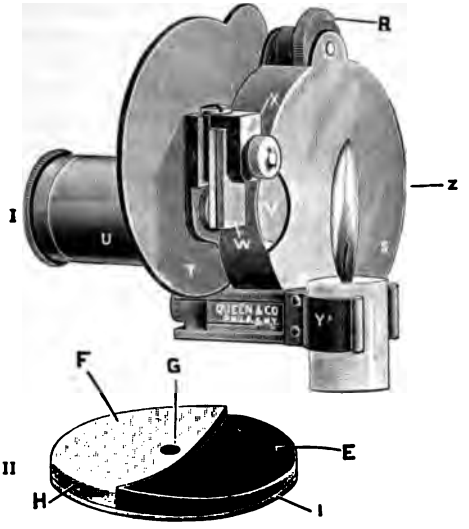


FIG. 232.—DARE'S HEMOGLOBINOMETER.

(Parts assembled as when in use. About one-half actual size.)

I.—R. Milled head, which rotates a rubber-covered cylinder that, in turn, acts upon the color-comparison prism, V. S. The metallic case containing the color-comparison disc, V. T. The metallic wing that receives the telescoping camera tube U, and, when not in use, rotates eccentrically into place over the back of the metallic box S. U. Telescoping camera tube. V. Visible portion of the disc that carries the color-comparison prism. The space indicated is secured by cutting out a semicircular piece of the metallic front, S. Through this opening the light passes to the color-comparison prism. W. White glass of the pipet. X. Pipet clamp. Y. Spring clamp candle-holder. The leader from Z indicates the point on the side of the metal case, S, where the graduation on the disc, V, is visible, and where the reading is taken.

II.—*Disc Carrying the Color-comparison Prism.* E. Prism of colored glass. F. Semicircle of white glass, upon the edge of which, at H, is etched the graduation. I. White glass backing the color-comparison prism, E. G. Opening through center of disc to receive the pivot of the casing, which acts as a hub around which the disc is rotated.

collecting the blood (II, Fig. 233 ; X W, Fig. 232) is removed from the tongue in which it fits ; the milled head controlling the screw that holds the two pieces of glass (A, B, Fig. 233 II) is turned far enough to release the glass plates ; these are separated, cleaned with alcohol, and polished. It is important that they should be free from all foreign substances, and, above all, that they should not be greasy. After thorough cleansing they are

returned to their proper position in the following manner: The observer will have noticed that one of the glasses (the white glass) has cemented upon it a thin plate of glass, which extends to within seven millimeters of one end. If the second glass be laid upon the thin plate, a space will be formed at one end of, and between, the two glass plates. This is the capillary space, into which the blood is to be received; it is shown at D, figure 233. The glass plates are placed in the clamp with the end containing the space projecting outward, and are secured in this position by tightening the retaining screw by means of the milled head.

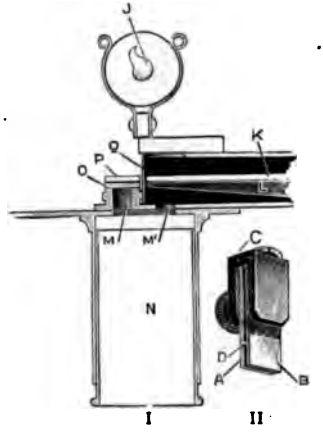


FIG. 233.—DARE'S HEMOGLOBINOMETER.

I.—*Horizontal Section, Viewed from Above.* J. Candle in spring clamp. K. White glass on the back of the prism. L. The colored prism used for comparison with the blood, and shown at E in figure 232. M. The opening through which the blood is viewed. M'. The opening through which the comparison color is visible. N. The telescoping camera tube, through which the two apertures, M' and M, are viewed in making the comparison. O. Transparent glass of the pipet. P. White glass of the pipet. Between the transparent glass, O, and the white glass, P, is the capillary space containing the blood. Q. Metal septum interposed between the blood pipet and the comparison color.

II.—*Automatic Pipet.* A. White glass. B. Clear glass. C. Pipet clamp in which at C' is a groove into which the tongue on the stage slides. D. Capillary chamber or pipet for receiving the blood. To the left and slightly behind is shown a milled head controlling the screw that clamps the glasses.

The white glass should be on the side next to the milled head. The clamp with the two glass slips is as shown at II, figure 233. The instrument is now ready for use.

The finger-tip or the lobe of the ear is prepared in the usual way, and the blood is drawn as already directed (p. 397). The free end of the glass slips (A, Fig. 233, II) is now presented to the drop of blood, which at once enters and fills the capillary space, D, figure 233. If the instrument has been properly cleansed, the pipet at once fills to all its margins. Care must be taken to pre-

vent the blood from flowing over the glasses, but in case such an accident occurs, the excess of blood can be readily wiped off. The clamp is at once placed in position, as shown at X, figure 232. When properly placed, the projecting glasses, with their intervening capillary space filled with blood, rest over the opening shown at M in figure 233. In this same sectional view the glasses are shown at O, P; the white glass is at P, the clear glass at O, and between them is the blood. Light the candle, which has already been placed in its proper position. The eye is placed to the drawn-out telescoping tube (N, Fig. 233; U, Fig. 232; in both instances the eye occupies the position of the Roman numeral I in the illustrations), and the line of vision is directed toward absolute darkness, with no intervening light, either direct or reflected, except that afforded by the lighted candle. Absolute darkness, such as is necessary for the von Fleischl instrument, is not required. A dark room is to be preferred; bright light is, of course, to be excluded, and the direction of the line of vision should at least be toward a lusterless black surface, such as is ordinarily afforded by a black coat. Looking through the tube N, figure 233 (the instrument being held as shown in Fig. 232, in which case the eye would be at I), the observer sees at the bottom of the tube two apertures (M and M′, Fig. 233), through each of which a more or less faint red or reddish-yellow light is seen. By referring to the diagram, figure 233, it will be apparent that the light coming from the candle, J, passes through the blood between the glasses, P and O, and is visible at M. Other rays of light, starting from the same point, pass through the glass comparison prism L, and are to be seen at M′. The two apertures, M and M′, are closely approximated; the milled head R (Fig. 232) is now turned one way or the other until the light passing through the glass comparison prism and visible at M′ is of the same color as the light coming through the blood and presenting at M. During all the manipulation the graduation has not been seen, unless the observer went out of his way to examine it; when the two colors have been matched, the reading is made on the side of the instrument, just behind the leader from the letter Z. The graduation, as in the other hemoglobinometers, is in percentage of the normal; its location on the disc is indicated at H, figure 232, II. The reading should be made at once on filling the pipet, as after twenty or thirty minutes contraction and shrinking of the clot occur, giving rise to a marginal illumination with concentration of the colored elements near the center, and thereby offering certain possibilities of error.

When the observation is completed, the clamp X, figure 232,

is removed, and the milled head is turned just enough to release the two glass slides, which are separated and cleaned at once. The ease with which the only part soiled is cleansed contrasts with the great difficulty ordinarily attending efforts satisfactorily to clean the automatic pipets and mixing chambers of the instruments devised by von Fleischl and Oliver.

Estimation of the Quantity of Hemoglobin by the Specific Gravity.—As a rule, the specific gravity of the blood indicates with a fair degree of accuracy the quantity of hemoglobin present, and hence may be utilized as one of the methods for hemoglobin estimation. As alteration in the density of the plasma can not be ignored, and as possible hydremia can not be overlooked, the specific gravity method will always be open to sources of error. In diabetes the evident high specific gravity (not uncommonly 1060 or over) would be misleading; under such conditions the method is not applicable. Conditions increasing the density of the blood by abstracting the water, thereby raising the plasmatic specific gravity, vitiate the results obtained by this method. The following table, from Hammerschlag, gives the hemoglobin value of specific gravities between 1033 and 1060:

Specific Gravity.	*Hemoglobin.*	*Specific Gravity.*	*Hemoglobin.*
1033–1035	25–30 per cent.	1048–1050	55–65 per cent.
1035–1038	30–35 "	1050–1053	65–70 "
1038–1040	35–40 "	1053–1055	70–75 "
1040–1045	40–45 "	1055–1057	75–85 "
1045–1048	45–55 "	1057–1060	85–95 "

To Determine the Specific Gravity.—The simplest procedure for the determination of the specific gravity of the blood is by the benzol-chloroform method of Hammerschlag. Chloroform has a specific gravity much higher than blood (1525), benzol much lower (0889), and as the two fluids are miscible in all proportions, any intermediate specific gravity is readily obtained. The instruments needed are a urinometer or hydrometer jar and an accurate urinometer, the scale of which should reach at least 1060. A mixture of chloroform and benzol is made having a specific gravity of about 1060; the blood is obtained in the usual manner and is drawn into a capillary tube, such as the Thoma-Zeiss pipet or Gowers' pipet, or any similar tube; care must be taken that no air is permitted to enter the column of blood. From the pipet a drop is gently and slowly ejected into the chloroform-benzol mixture, being careful to exclude air. If the hydrometer jar containing the chloroform-benzol mixture has been properly cleansed and dried, the drop of blood will not adhere to its wall. The blood, not being miscible with the reagents, forms a drop,

which floats on the surface of the fluid. Benzol is added, with careful, repeated stirring; the addition is continued until a density is reached in which the drop neither rises to the top nor sinks to the bottom: in other words, the specific gravity of the fluid is made the same as the specific gravity of the drop of blood. The specific gravity of the fluid is now taken, and the result obtained is, of course, the specific gravity of the blood. From this specific gravity the percentage of hemoglobin may be calculated.

Remarks on Hemoglobin Methods.—Of the various methods given, that devised by von Fleischl has received most general acceptance. It is said that the von Fleischl instrument is unreliable for very low percentages of hemoglobin; the source of error is best met by using two measures of the blood, secured by filling two pipets and emptying both into the mixing chamber. The resulting reading is halved. Yarrow and Hitchens * have compared results obtained by the specific gravity method, by Gowers', von Fleischl's, and Oliver's instruments, and by the hematoscope of Henocque, and after an exhaustive investigation these authors conclude that the instrument of Oliver is by far the most accurate. Next to this method they prefer calculations based upon the specific gravity, and look upon von Fleischl's and Gowers' instruments as constantly liable to error. It would possibly be premature to express a definite opinion with regard to the convenience and reliability of Dare's hemoglobinometer. Dr. Dare has made a large number of blood examinations, and has compared the results with those of the Gowers and the Oliver instruments, and has found that his instrument yields the most constant results. In the few examinations and demonstrations of the Dare hemoglobinometer that the author has had an opportunity to see he was impressed by the fact that two individuals could read so close together, as variations of two, three, four, and five per cent. were infrequent. The same workers would, in reading the von Fleischl and Oliver instruments, differ to the extent of from five to ten per cent.

The term **percentage of hemoglobin** means the percentage of the normal. If the reading is 100, the hemoglobin is normal; if, however, the reading is 80, there is eighty per cent. of the normal, or twenty per cent. less than normal; if the reading is 120, there is twenty per cent. more than normal.

The **color-index** is the relative richness of each erythrocyte in hemoglobin. As previously stated, the percentage of hemoglobin estimated by the instruments commonly at hand is the percentage

* "University Medical Magazine," October, 1899.

of the normal. If in a blood examination we find 5,000,000 red blood-cells and 100 per cent. of hemoglobin, it is evident that both the erythrocytes and the hemoglobin are normal, and the color-index is said to be 1. If, however, we have 2,500,000 red blood-cells and 50 per cent. of hemoglobin, it is evident that, while there is a great reduction in red blood-cells, there is also a proportionate reduction in hemoglobin; each red blood-cell, however, contains its normal percentage of hemoglobin; it is thus seen that the corpuscular richness of the cells present is the same as in health, therefore the color-index is normal—1. If, on the other hand, as in chlorosis, 4,000,000 red blood-cells are present (assuming as before, for convenience in calculation, that the normal is 5,000,000), then the number of erythrocytes present is 80 per cent. of the normal. If the blood shows the presence of 50 per cent. of the normal amount of hemoglobin, it is evident that the hemoglobin is much more reduced than the erythrocytes; in other words, the color-index is low. The exact color-index is obtained by dividing the percentage of hemoglobin by the percentage of erythrocytes: in the instance given, $\frac{50}{80}$, or $\frac{5}{8}$ (or, in decimals, 0.625), would be the color-index. From the foregoing it will be seen that the color-index may be worked out by the following formula:

$$\frac{\text{Percentage of hemoglobin}}{\text{Percentage of erythrocytes}} = \text{Color-index.}$$

COUNTING BLOOD-CELLS.

The Red Cells.—*The Thoma-Zeiss Hemocytometer.*—This apparatus consists of:

1. A capillary tube of glass, about fifteen centimeters long, expanding in the upper portion into a bulb, in which lies a small glass ball. (Fig. 235.) The lower portion of the tube is graduated in tenths, from 0.1 to 1, while just above the mixing chamber is the mark 101, indicating that, if filled with blood to the mark 1, and then with some other fluid to 101, the fluid above the point 1 will represent a dilution of 1 part in 100.

2. A counting chamber, composed of a heavy glass slide, the center of which is formed into a circular cell by a rim of glass; in the middle of the cell is a circular glass platform. (See A and C, Fig. 236.) When a cover-glass is placed over the cell, the space between the cover-glass and the surface of the counting platform is 0.1 mm. The counting platform has on the center a space ruled in squares, the side of each square being $\frac{1}{20}$ of a millimeter. The cubic capacity, then, of the space sur-

rounded by each ruling and covered by the cover-glass is equal to $\frac{1}{20}$ mm. $\times$ $\frac{1}{20}$ mm. $\times$ $\frac{1}{10}$ mm., or $\frac{1}{4000}$ of a cubic millimeter. The small moat between the platform and the rim receives the overflow of fluid.

A puncture is made in the finger or in the lobe of the ear, as already directed, and the blood is sucked into the capillary tube until it reaches the mark 1 ; after wiping the end of the tube in order to remove the excess of blood, a three per cent. salt solution, or other acceptable diluting fluid, is sucked into the tube until the fluid has arisen to the point marked 101. The contents of the tube being thoroughly mixed by shaking, the fluid below the bulb is then expelled, the point of the tube is wiped, and a drop of the diluted blood is placed on the ruled platform of the counting slide ; a cover-glass is then cautiously laid upon the drop, care being

FIG. 234.—THOMA-ZEISS HEMOCYTOMETER.

As shown in the illustration, the different parts are packed in a velvet-lined case for safe transportation. In the center of the case is a glass slide, which contains the counting chamber. As illustrated, the two pipets—one for the erythrocytes and one for the leukocytes—are contained in the single case. The receptacle for thick covers is just under the center of the slide.

taken that the cover does not slip to either side. If a globule of air forms between the cover and the counting platform, the cell and cover should be cleaned and the attempt should be repeated, the cover-glass being so adjusted that there are no air-bubbles present.

The preparation should be rejected if the liquid makes its way between the cover-glass and the external rim. The cover-glasses used in ordinary microscopy are not suited for use with this instrument ; they are rarely flat, cup easily, and in either case may give misleading results. Only the heavy covers that accompany the instrument should be used. The thick cover-glass and the depth of the cell preclude the use of high-power objectives ; the most convenient lens for the count is a ¼-inch objective. The micro-

scope is so adjusted that the stage is perfectly level. The slide is placed upon the stage and the ruled areas are found and centered by the use of a 1-inch or a ⅔-inch objective. The higher power (¼-inch objective) is now thrown in the optic axis of the instrument, and, without looking through the eye-piece, the objective is racked downward until it almost touches the cover-glass. The eye is then

FIG. 235. — CAPILLARY MIXING TUBE OF THE THOMA-ZEISS APPARATUS. — (*Jaksch.*)

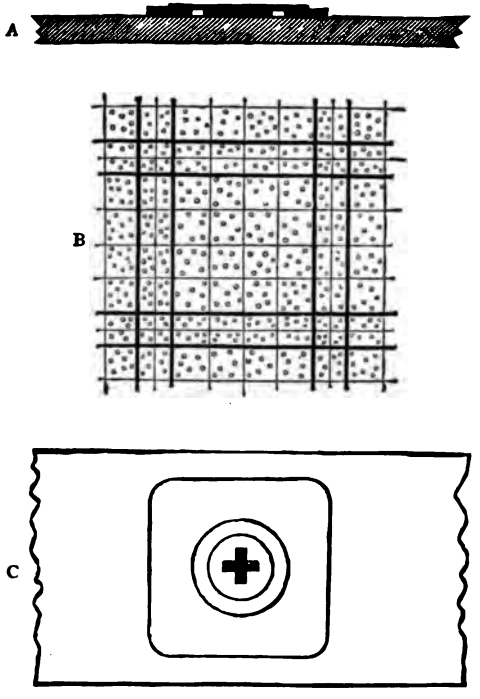


FIG. 236.—COUNTING CHAMBER OF THE THOMA-ZEISS HEMOCYTOMETER.—(*Landois.*)

A. Sectional view. On the upper surface is shown cover-glass in position. Beneath the center of the cover is a glass platform, upon which is ruled the divisions shown in the surface view, C. The space between the cover and the ruled platform is 0.1 mm. On each side of the ruled platform is shown the moat that prevents the fluid from reaching the outer disc, upon which the cover-glass rests. B. Appearance of the ruled surface under microscope and showing uniform distribution of the red cells as they should appear in a properly prepared dilution.

placed at the eye-piece and the illumination is perfected, after which an accurate focus is secured by slowly focusing upward. At first the corpuscles may be in different focal planes, and it is

therefore best to allow the instrument to remain quiet for a few minutes until the cells have been deposited upon the counting platform. The cells should be evenly distributed, as shown at B in figure 236. If they are clumped and not uniformly distributed over the counting platform, the mixing has been inefficient, and the mixing tube must be cleaned and the whole process repeated. Find the number of corpuscles in at least twenty squares; divide this number by 20 in order to find the number in a single square, and multiply the result by 4000 ($\frac{1}{4000}$ c.mm. being the contents overlying a square), and this figure by 100, the degree of dilution, and the result will be the number of blood-corpuscles contained in one cubic millimeter of blood. Example: A count of twenty-five squares gives a total of 284 red cells: $\frac{284}{25} = 11.36$, the average number of erythrocytes in each square. As it requires 4000 times the cubic capacity of one square to equal a cubic millimeter, the number of cells in one square, 11.36, must be multiplied by 4000; allowance must now be made for the dilution (100), the final calculation being $11.36 \times 4000 \times 100 = 4,544,000$, the number of cells in one cubic millimeter of blood. In recording the corpuscular richness (erythrocytes or leukocytes) of the blood it is customary to give simply the number without stating the quantity of blood—*c. g.*, "4,544,000 red cells" means that that number was found in one cubic millimeter of blood.

Counting White Corpuscles.—To count the white corpuscles in a dilution such as that used for the red would require more time and a much larger ruled space than is available in the Thoma-Zeiss instrument. For this reason a lower dilution is used,—1 : 10, instead of 1 : 100,—and, for diluting, a 0.33 per cent. solution of acetic acid, which destroys the red blood-cells, at the same time making the white cells more distinct. The method, with the foregoing exceptions, is as given for the red; in the calculation, however, after multiplying the number in one square by 4000, the final result is attained by multiplying by 10, the amount of dilution, instead of by 100, as in estimating the erythrocytes.

Of the many diluting solutions that have been recommended, either of the following will be found useful:

Toisson's Solution.

Methyl-violet,	0.025	gm.
Sodium chlorid,	1.0	"
Sodium sulphate,	8.0	"
Glycerin,	30.0	c.c.
Distilled water,	160.0	"

Sherrington's Solution.

Ehrlich's purified methylene-blue,	0.1	gm.
Sodium chlorid,	1.2	"
Neutral potassium oxalate,	1.2	"
Distilled water,	300.0	c.c.

The anilin dyes contained in the foregoing solutions stain the leukocytes, and thereby facilitate their enumeration.

Differential Counting:—Dried and fixed films are stained by Ehrlich's stain, and are mounted as already directed. Then the leukocytes are counted by traversing, in straight lines, more or less of the stained field, carefully avoiding going over the same point twice, and counting at least 1000 leukocytes. A mechanical stage greatly facilitates the count. On a piece of paper by the side of the microscope are arranged columns, at the top of which are written the forms of leukocytes; after counting the required number, the columns are added up and the percentage of each form present is calculated.

Differential counting of diseased red cells is sometimes resorted to, and may be done in the same manner.

Hematocrit.—This instrument (see Fig. 80, p. 120) readily enables one to estimate the *volume of the red corpuscles.* It consists of:

1. Two glass tubes, 50 mm. long, with a lumen of 0.5 mm., and graduated into 100 parts. (Fig. 237.)

FIG. 237.—HEMATOCRIT TUBE. (Twice natural size.)
The tube as illustrated has been filled with blood and rotated, as directed in the text, until the erythrocytes have collected at one end, occupying 45 degrees (or graduation-marks). This, multiplied by 100,000, gives 4,500,000—the number of erythrocytes to the cubic millimeter of blood.

2. A metallic frame (Fig. 238), in which the glass tubes are fastened—on the outer side by a metallic cup in the frame, and at the proximal extremity by a spring, which is attached to a hollow metal cylinder, which projects downward from the center of the frame, and by means of which the frame can be made to rotate on a vertical axis. The cups receiving the ends of the glass tubes contain rubber washers that also act as cushions.

3. A vertical support, which can be made to rotate. A speed of at least 10,000 rotations a minute is necessary.

4. A metallic box, to be fastened to a table, and containing the machinery by which the vertical support is made to rotate.

To Use the Hematocrit.—One of the graduated tubes, previously well cleaned, is attached by means of a short piece of pure rubber tubing to a medicine-dropper. The bulb of the dropper is gently compressed, and the end of the graduated tube is presented to the escaping blood; the compressed bulb of the pipet is slowly

FIG. 238.—ROTATING FRAME OF THE HEMATOCRIT.

The tube on the right is in position; the tube on the left shows the graduation and the direction which the smaller end should take when in position. The entire metal frame is to be placed on the vertical support, as described in the legend of figure 80, page 120.

released, thereby sucking the blood into the capillary tube. As soon as the tube is full, the end in the drop of blood is pressed against the patient's thumb, without withdrawal from the drop, and the rubber tube and the medicine-dropper are removed. Figure 240 and the legend explain the usual method by which

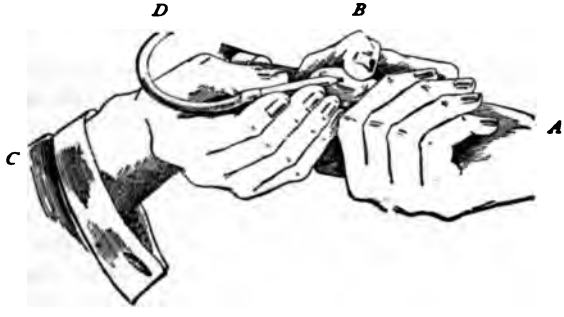


FIG. 239.—A METHOD OF FILLING THE CENTRIFUGE TUBE.

A. The hand of the patient. The thumb has been punctured and is firmly supported by the left hand of the operator, as shown at *B*. *C*. The right hand of the operator, holding the capillary tube, to which is attached a rubber tube, *D*. To the latter suction is applied, thereby drawing the blood up into the capillary tube. By some workers this method is preferred to that recommended in the text.

the tube is filled. If but one tube is to be filled, the other should be in place in the rotating frame of the instrument, to act as a counterpoise to the charged tube. As soon as the latter is filled, it is placed in position in the frame, which is at once rotated at the rate of 10,000 revolutions a minute for two minutes. The

red blood-corpuscles collect in the distal extremity of the tube, the leukocytes in the center, and the liquor sanguinis in the proximal portion. Find the number of degrees the red cells occupy, and, as each degree has been found to represent approximately 100,000 cells to the cubic millimeter, the addition of five ciphers gives the number of red cells to the cubic millimeter. Thus, if the red cells occupy fifty graduations on the scale, there are 5,000,000 red cells to the cubic millimeter. (See Fig. 237.)

It is apparent that the result is in volume of red cells, and not the number that must be obtained by a calculation that does not take into consideration the size of the cells. When the red cells are larger than normal, the greater volume would give a misleading result. The reverse is equally true.

GENERAL PATHOLOGY, COMPOSITION, AND STRUCTURE OF THE BLOOD.

The circulating normal blood consists of a fluid portion (the **liquor sanguinis**) in which are suspended the solid elements—the blood-corpuscles or blood-cells. The liquor sanguinis is probably identical—or practically so, at least—with the circulating medium outside the blood-vessels in the primitive lymph-spaces, and which passes to the lymph-glands and is returned to the circulation. As a part of the blood, the liquor sanguinis is more than a mere vehicle for the transportation of the solid elements, and with its complex chemistry is the essential food-carrying body to the tissue at large. It is composed of the elements out of which serum and fibrin may be formed; and while this separation, so far as the plasma is concerned, is largely a death change, still, evidence is not wanting to show that fibrin formation may be an essential element in the protection of the organism and in repair. Thus, the distinct wall of fibrin that forms around infected areas or covers an infected serous surface, such as a pleura, and through which osmosis and the absorption of bacterial products are reduced to a minimum, acts not only as a scaffold upon which embryonic tissue, and eventually granulation tissue, can build the framework which is to repair the injured part, but also as a prophylactic, limiting membrane, through which infection travels only with the greatest difficulty. Again, of all the structures produced within the body, fibrin offers the greatest resistance to many of the injurious incidents to which the tissues are liable; the constant pressure of the circulating blood, as in an aneurysm, may lead to atrophy and to the disappearance of bone, unless conditions arise that determine the intervention of a wall of

fibrin, through which, not uncommonly, we may hope for a cure. The exact factors that enter into the chemistry of fibrin formation are not known; although the third corpuscle would seem to bear some causative relation to the process, the character and extent of such influence remain one of the unsolved problems of physiologic chemistry.

An excess of fibrin, or, more truly, of fibrin-forming elements, constitutes **hyperinosis**—a condition present in pregnancy, and occasionally in chlorosis and other forms of anemia. **Hypinosis,** or reduction in the fibrin-forming elements, is sometimes observed in leukemia and pernicious anemia. In addition to the influences modifying the amount of fibrin, there are marked differences in the rapidity with which it is formed. As a rule, intravascular coagulation begins shortly after death. To this, however, there are notable exceptions. The author recalls a case of pernicious anemia in which, at the postmortem, made twelve hours after death, the blood had not coagulated. After removal from the cardiac cavities a quantity collected in a jar for later study developed a satisfactory coagulum. The blood is less coagulable in hemophilia, in which disease its coagulability may be, in some cases, increased by the administration of calcium salts, while in other cases the local application or the internal administration of these agents fails to influence the condition. Lessened coagulability is present in the blood after death from poisoning by carbonic acid or by carbon monoxid and in some cases of asphyxia. Snake-venom and bacterial products lessen the coagulability of the blood.

Hydremia is a condition in which the blood contains an excess of water. After a hemorrhage the volume of blood is made up by the abstraction of fluid from the tissues at large, and consequently there is a more or less temporary hydremia. When it is reasonable to believe that there is an increased amount of blood, and that the increased quantity is due to the addition of water or saline solutions, as after the injection of a large quantity of normal salt solution, the condition is called **hydremic plethora.** Under ordinary conditions hydremia quickly disappears, as a result of the excretion of water by the emunctories, particularly the kidneys.

Anhydremia is the reverse of hydremia. The lessened amount of water present in the blood usually results from its rapid extraction, although it is conceivable that a diminished supply would induce the same condition. The concentration is usually brought about by the discharge of fluid by the skin, intestine, or kidney. As the principal constituent so removed is

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water, it is this element that is reduced. As a rule, anhydremia, like hydremia, is temporary. In the former condition the tissues quickly supply the requisite amount of fluid.

In a number of morbid conditions the blood plasma contains abnormal bodies or normal constituents in abnormal quantities. A small quantity of fat is present in normal blood; occasionally, however, as in alcoholism, diabetes, and a few other conditions, it may be markedly increased, producing a condition called **lipemia.** The fat may be recognized in the freshly drawn blood as small, highly refractile granules, which not uncommonly manifest active movement. The examination is conducted as already directed. (See p. 397.) Dry spreads fixed in osmic acid (pp. 48 and 49) will show the blackened fat droplets. (See also Demonstration of Fat, p. 243.) The serum obtained by the centrifuge may contain enough fat to render it turbid. The small quantity of glucose normally present in the blood is markedly increased in diabetes, in which disease it may be present to the extent of 0.7 per cent. instead of the normal, 0.117 per cent. An increased amount of sugar in the blood is called **glycemia.** In leukemia, in pneumonia, in some forms of anemia, and at times in Bright's disease there is an increase of uric acid, or, more properly, of uric acid salts, in the blood. In gout the increase in urates (**uratemia**) is most marked.

The presence of bile pigments in the blood (**cholemia**) is the essential phenomenon of jaundice (p. 234). Clinicians recognize a form of intoxication which has long been termed **uremia.** At one time this was presumed to be due to the presence of an excess of urea in the blood. Later investigations have shown, however, that no quantity of urea, however large, introduced into the circulation reproduces the clinical picture of the uremia. Blood plasma also contains certain globucidal bodies destructive to red blood-cells of other animals. The bactericidal and antitoxic bodies in the blood have already been considered. (See pp. 155 to 159.)

Recent investigations, both experimental and clinical, seem to indicate that a study of the freezing-point of the blood may be of value in certain cases. Normal blood freezes at about 0.56° to 0.58° (C.), below the freezing-point of distilled water. Agents causing renal irritation or necrosis, such as cantharides, and morbid conditions associated with renal insufficiency, may lower the freezing-point to 0.6° or 0.7° (C.). The removal of the kidney similarly influences the freezing-point.

The so-called solid constituents of the blood are the corpuscles: the red, or erythrocyte; the white, or leukocyte; and the third corpuscle—blood-platelet, or hematoblast.

The red blood-cell, or **erythrocyte**, of man is a smooth, highly elastic, biconcave disc, which does not possess a nucleus. From seventy to eighty per cent. of the erythrocytes possess an average diameter of 7.5 μ. Of the remaining twenty per cent. about half are slightly larger, and the remaining cells slightly smaller, than the average given. In the normal blood, cells smaller than usual are probably more frequent than the larger cells. The smaller cells usually measure between 6 μ and 7 μ, although cells measuring less than 4 μ (dwarf cells) may occasionally be observed. The larger cells are more conspicuous in infancy, and are rarely seen after adolescence. In a number of morbid processes abnormal form and size constitute important alterations. In certain anemias many of the cells are small (**microcytes**); the condition is called **microcytosis**, or **microcythemia.** In some instances a varying number of the erythrocytes possess diameters of 8 μ or 9 μ, or are even larger; an occasional cell may attain a diameter of 15 μ. Such cells are called **macrocytes**, or **megalocytes**, and the condition is known of as **macrocytosis**, or **macrocythemia.** Microcytes are not uncommonly spheric, and in macrocytes the biconcavity is often inconspicuous or absent. Microcytosis and macrocytosis are frequently associated. The small hemal element described by Eichhorst is really an irregularly staining microcyte from 2.5 μ to 4 μ in diameter. It differs from the usual microcyte in the intensity with which it stains.

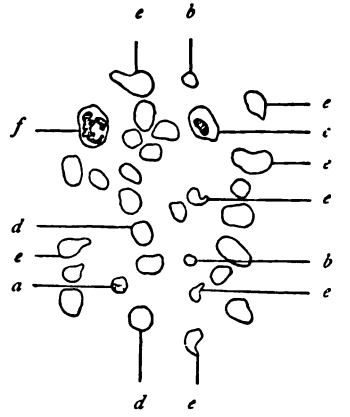

FIG. 240.—DIAGRAMMATIC REPRESENTATION OF VARIOUS FORMS AND SIZES OF RED CELLS.—(*From a case of pernicious anemia reported by Dr. J. C. DaCosta, Jr.*)

a. Erythrocyte (introduced to give an approximate idea of the size of other cells). *b*, *b*. Microcyte. *c*. Megaloblast. *d*, *d*. Macrocyte (larger macrocytes are also outlined, some of which are poikilocytes). *e*, *e*, *e*, *e*, *e*, *e*, *e*. Poikilocytes; other poikilocytes are also shown. *f*. Finely granular oxyphile (polymorphonuclear) leukocyte. The granules are not shown, but the extreme irregularity of the nucleus is indicated.

FIG. 241.—TYPES OF RED BLOOD-CELLS; ALSO LEUKOCYTES, AS AT *a*.—(*Landois.*)

As a result of disease, erythrocytes may change their form,

becoming ovoid, pyriform, knobbed, bobbin-shaped, etc. Cells showing such abnormality in form are called **poikilocytes,** or **schistocytes**; the condition is called **poikilocytosis.** Microcytes and macrocytes, as well as the nucleated forms to be considered later, not uncommonly show more or less irregularity in shape, and may be properly considered as poikilocytes. It is possible, by error in technic, to produce a distortion of the erythrocytes, which may mislead the uninitiated. If, in making the cover-glass spreads, as already directed, the two cover-glasses (p. 398) be left in contact too long, the act of separation may stretch the erythrocytes so that one diameter will be greater than another, a condition frequently observed in poikilocytosis. A careful study of such a field will show that the cellular distortion leads to an elongation of all the affected cells in one direction, a condition never observed in true poikilocytosis.

FIG. 242.—POIKILOCYTES.

Crenation is an appearance closely resembling poikilocytosis, but develops after the blood has been drawn. Crenated cells are irregular, and show knobbed projections from their surfaces associated with more or less shrinking of the protoplasm; by some it is believed that crenation is the extravascular analogue of intravascular poikilocytosis.

Early in fetal life the **nucleated red blood-cells** normally present at that period begin to disappear, and at birth, or shortly after, are no longer present in the normal blood. In certain morbid conditions, however, they form conspicuous hemal elements. It is usually held that at some stage in its evolution the red blood-corpuscle possesses a nucleus, which disappears before the cell assumes the function of a hemal cell. Exactly how this disappearance of the nucleus is accomplished has not been accurately determined. According to some observers, the nucleus disappears by extrusion, while others think it is removed by a process of absorption or of disintegration. The nucleated cells seen in the blood are of different sizes, justifying to a certain extent the division into three kinds.

FIG. 243.—CRENATED RED BLOOD-CORPUSCLES.—(*Landois.*)

Often seen in improperly fixed blood slides, in freshly drawn blood after prolonged study under the microscope, in urine, etc.

Normoblasts are nucleated red cells the diameter of which is approximately that of the normal erythrocyte. The size of the nucleus varies, and it is usually eccentric in location. It is rich

in chromatin, stains with intensity by the usual nuclear stains, and not uncommonly shows a fine, intranuclear net. Occasionally, the nucleus will be found partly outside of the protoplasm—a condition that suggests its extrusion. Sometimes, in properly fixed preparations evidences of mitosis may be present, or the cell may contain two or even three nuclei; these may appear distinct and separate, while in other cells connecting bands of chromatin may be recognized. The perinuclear protoplasm contains more or less hemoglobin, and hence stains with the acid anilin dyes. The outline of the cell is commonly uneven, so that a varying percentage of these cells may be properly called nucleated poikilocytes, or **poikiloblasts.**

The **microblast** is a small nucleated form, smaller than the normal red blood-cell; both nucleus and protoplasm are diminished in quantity, although occasionally microcytes may be found possessing a nucleus as large as the nucleus of the normoblast. Intranuclear changes are infrequent. The perinuclear protoplasm is not uncommonly shredded, and the cell is regarded by most observers as a degenerated necrobiotic or fragmenting form of the normoblast.

Megaloblasts, or **macroblasts** (also called *gigantoblasts*), are abnormally large red cells possessing nuclei; the diameter of such cells usually exceeds 10 μ, and may attain 16 μ. The nucleus is relatively large, but stains with less intensity than the nucleus of the normoblast. The perinuclear protoplasm is usually rich in hemoglobin. The cell not uncommonly shows degenerative changes, as indicated by the unevenness in staining and by the occurrence of vacuoles in its interior. Frequently such cells are irregular in conformation, and may be properly called poikiloblasts. The demonstration that unusually large red blood-cells (megalocytes or megaloblasts) may contain more hemoglobin than corpuscles normal in size possibly explains the fact that in certain diseases in which these cells are comparatively abundant the color-index may be high. (See Pernicious Anemia.)

In addition to abnormality in size and shape, certain necrotic alterations are sometimes present in the red blood-cells. By some, poikilocytosis is regarded as an evidence of necrotic change, and the endoglobular alterations about to be described are not uncommonly associated with, or terminate in, the production of poikilocytes. The central normally pale area of the corpuscle may increase in pallor, and may eventually lose all its coloring-matter; the periphery at the same time may show deepening of color. Sometimes hyaline or vacuolated spots appear in the periphery of the cell, or the cell becomes ovoid in

profile with a vacuole at one or both ends. A number of these changes, associated with solution of the hemoglobin and other soluble parts of the cell, have been grouped by Arnold under the name **erythrocytolysis,** or **plasmolysis.** Crenation, which ordinarily is not developed for some time after the blood is drawn, may be present immediately after shedding. The knob-like projections seen on crenated cells may break off (**plasmorrhexis**) and float free in the blood.

The number of red blood-cells normally present is approximately 5,000,000 in man and from 4,000,000 to 4,500,000 in woman to each cubic millimeter of blood. Blood containing more corpuscles than normal is said to show **polycythemia**; a reduction in the number of erythrocytes is called **oligocythemia.** Within the first twenty-four hours following birth a maximum of from 6,000,000 to 6,500,000 may be reached. The number is reduced by hemorrhage and by various anemias, which will be considered later. The number is reduced by prolonged exertion, and menstruation usually induces a slight decrease. The most marked diminution in number is seen in pernicious anemia, in which the oligocythemia may be extreme. Counts as low as 500,000 are not infrequent, and a minimum of 143,000 has been recorded.

Aside from the physiologic increase in the number already noted as present for a brief period after birth, little is known of the etiologic factors active in the production of **corpuscular plethora,** or polycythemia. Impeded circulation, or even the influence of gravity, may slightly increase the number of corpuscles present in a given area. In cyanosis and in cardiac lesions associated with peripheral stasis relatively high counts are not infrequent. The polycythemia observed in the cyanosis of congenital heart disease may be extraordinary, as in the case reported by Baunholtzer—9,447,000 erythrocytes, 160 per cent. of hemoglobin. As a result of the loss of fluid from the vascular system,—as by serous diarrhea, profuse sweating, excessive vomiting, etc.,—the temporary concentration of the blood increases the number of corpuscles present in a given quantity. The condition is, as a rule, temporary under such circumstances. An interesting form of polycythemia is that which develops during residence in high altitudes. As a rule, the maximum polycythemia resulting from this cause does not manifest itself for a month or more, but not infrequently within twenty-four hours after the ascent a notable increase in the number of red blood-cells may be observed. Solly records an instance in which a day's excursion was attended by an increase of 600,000 red cells. The total rise in the number of red cells may reach from twenty

to fifty per cent., not infrequently exceeding the latter. The erythrocruorin does not keep pace with the increase in red blood-cells, although the percentage of hemoglobin is usually augmented. Whether the polycythemia is due to an inspissation of the blood, to increased peripheral distribution, to more active blood production, or to the lengthened life of the red blood-cells has not been satisfactorily determined. The facts that the red corpuscles increase more rapidly than the hemoglobin, that there is an increase in the average diameters of the red blood-cells, and that the normoblast nuclei are found free in the blood, all favor the view of increased production of cells. The polycythemias of phosphorus-poisoning and carbon-monoxid-poisoning have not received any fully satisfactory explanation.

Structurally, the red blood-cell appears to be composed of two elements—a delicate reticulum or stroma, but partly soluble in water, inclosing spaces within which lies an albuminous soluble portion of the cell, which contains the hemoglobin. This part is freely soluble in water. **Hemoglobin**, or erythrocruorin, is the soluble pigment to which the color of the blood is due. It is a complex proteid, readily decomposable into a number of so-called reduction products. Some of these have been considered with pigments. (See Pigmentary Infiltration, p. 233.) The amount of hemoglobin present in the blood varies within certain limits. It may be said that, approximately, 100 gm. of blood contain about 14 gm. of hemoglobin. It will be recalled that in considering the methods of estimating the quantity of hemoglobin the results are commonly given in percentages of the normal. It will, therefore, be apparent that when a hemometer or hemoglobinometer records 100 per cent., the quantity indicated is 14 gm. in 100 gm. of blood. Hemoglobin combines with oxygen to form oxyhemoglobin, which, when carried to the tissues, yields its oxygen, the hemoglobin remaining as reduced hemoglobin. With CO it forms a more stable compound, called carbon-monoxid-hemoglobin. The carbon monoxid compound is not readily dissociated, and hence in poisoning by carbon monoxid the oxygen-carrying power of the blood is held in abeyance as a result of the inability of the oxygen to displace the more firmly combined gas. Methemoglobin, hematoidin, hemin, and other pigments derived from the blood have been considered with pigments where they possess any pathologic significance, and for further consideration the reader is referred to text-books on physiology. As the amount of hemoglobin present in the corpuscles largely influences their specific gravity, the latter has been utilized as a method of determining the percentage of hemoglobin present. (See p. 412.)

When the quantity of hemoglobin falls below the normal, the condition is called **oligochromemia.** Hemoglobin is diminished in all anemias, and not uncommonly its diminution is in direct proportion to the reduction in the number of red blood-cells; in other instances the corpuscular richness in hemoglobin may be greatly reduced without any marked reduction in the number of red blood-cells. These alterations in the quantity of hemoglobin present will be considered with more detail when dealing with individual forms of anemia.

Leukocytes.—The white cells of the blood, unlike the red, are found in a number of forms, the relationship of one form to another not having been clearly established. Unlike the red blood-cells, the leukocytes are nucleated, and normally contain no hemoglobin. The proportion of leukocytes to red blood-cells varies widely in health, the variation depending upon the temporary rise and fall in the number of leukocytes, irrespective of coincident changes in the number of erythrocytes. All authors recognize these fluctuations in the number of leukocytes, but all are fairly agreed that the relative proportion of leukocytes to red blood-cells is 1 of the former to 500 or 600 of the latter. The various forms of leukocytes exist in the blood in fairly constant proportions. The different forms, the general descriptions, and the percentages present in the normal blood will be found in the accompanying table. (See pp. 430 and 431.) In addition to the groupings there given, several of which possess only historic interest, we must recognize that certain cells are essentially hemal and that others are essentially celomic, although each not uncommonly invades the other's territory. The normal number of leukocytes in a cubic millimeter of blood approximates from 6000 to 9000.

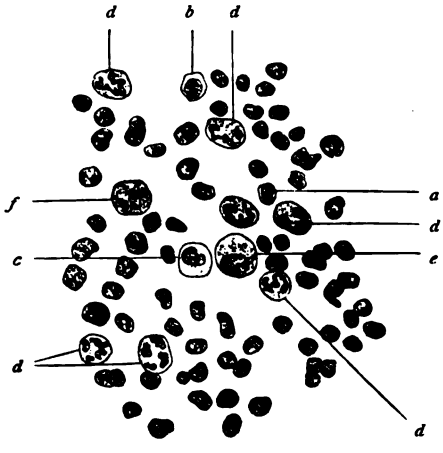

FIG. 244.—DIAGRAMMATIC REPRESENTATION OF LEUKOCYTES.

a, *b*. Lymphocytes. *c*. Hyaline cell. The cell outlines are not so sharp as indicated. *d*, *d*, *d*, *d*, *d*. Finely granular oxyphile (polymorphonuclear) leukocytes. *e*. Myelocytes. *f*. Coarsely granular oxyphile (eosinophile) leukocytes.—(*From splenomedullary leukemia; drawn by Dr. J. C. DaCosta, Jr.*) See Fig. 188, p. 286; Fig. 189, p. 287.

In many conditions a reduction in the number of leukocytes (**hypoleukocytosis, leukopenia,** or **leukocytopenia**) occurs. Such reduction in the number of leukocytes is seen at times in protracted febrile processes, unassociated with pyogenic infection, in typhoid fever occasionally, rarely in pneumonia, and at times in tuberculosis. Blum* believes that the leukopenia seen in typhoid fever, influenza, and certain cases of tuberculosis is due to involvement of the lymphoid tissues of the alimentary canal, and particularly in the intestine. Sometimes in pernicious anemia a marked fall in the number of leukocytes occurs. This phenomenon is not a constant feature of any disease. The leukocytes are reduced by starvation, and preliminary to leukocytosis—particularly to that form called inflammatory—a temporary leukopenia is sometimes present. In marked cases of hypoleukocytosis the number of leukocytes may be 600 or even less to the cubic millimeter of blood. The essential cause of this condition is not known. It is held by some that there is a faulty production of leukocytes; by others, that there is an increased destruction—**leukolysis.** It is not improbable that both factors are operative. Faulty distribution may have something to do with absence of leukocytes from the peripheral circulation, the normal distribution being altered as a result of leukocytic accumulation in the large viscera, particularly the lung.

In addition to the reduction in number, leukocytes not uncommonly show evidence of extensive **karyolysis.** One of the most marked karyolytic changes is that seen in the finely granular oxyphile cell in pyogenic processes. The pus-cell, with its many irregularities in protoplasm and nucleus, is a finely granular oxyphile cell showing the results of karyolytic change brought about by the activity of the bacterial toxins. In pronounced anemia, or in other conditions associated with blood destruction, the leukocytes may contain fragments of red blood-cells and particles of pigment derived from various sources; such cells are called *melaniferous leukocytes.* Abnormality in color, reaction, position, size, and distribution of leukocytic granules is not uncommonly present; such variations are probably evidences of degenerative change.

Leukocytosis.—As already indicated, a wide variation in the number of leukocytes is compatible with health. Efforts to draw absolutely exact limits beyond which the normal fluctuations do not go have been, for the most part, illusive. If we adopt a comparatively low standard, such as 8000 or 9000, or even 10,000,

* "Wiener klin. Woch.," April 13, 1899.

Wharton Jones. 1846.	Max Schultze. 1865.	Metschnikoff.	Ehrlich.		Kanthack and Hardy.	Hayem.		Percentage Present in Normal Blood.
Non-granular nucleated cells.	Small round cell I.	Lympho-cyte.	Lympho-cyte	Small	*Lympho-cyte.*	Leuco-cytes of the first variety.	Small type.	15 to 30.
	Large round cell II.	Macro-phagocyte		Large	*Hyaline cell.*		Large type.	2 to 6.
Granule cells finely granular.	Cells with finely granular protoplasm.	Micro-phagocyte.	Cells neutrophile in man, amphophile in some of the lower animals.		*Finely granular oxyphile cells.*	Leucocytes of the second variety.		60 to 72.
Granule cells coarsely granular.	Cells with coarsely granular protoplasm.	Eosino-philes.	Leucocytes with α granules.		*Coarsely granular oxyphile or acidophile cells.*	Leucocytes of the third variety.		Rarely over two per cent.; in childhood may reach 11 to 14 per cent.
			Cells containing γ granules. "Mastzellen."		*Coarsely granular basophile cells.*			Rarely if ever present in normal blood, present in celomic fluids and connective tissues.
Granule cells finely granular.	Cells with finely granular protoplasm.		Basophile cells with δ granules.		*Finely granular basophile cells.*			Rarely exceeds .25.
			Myelocytes. Marrow cells. ("Markzellen" of German writers).			Hypertrophied white cells.		Not present; found in bone marrow (red) and present in blood in leukemia.

* After Adami's table (Albutt's "Sys. Med.," vol. 1, p. 79);

LEUKOCYTES.*

Size.	Further Description and Remarks.
5 to 11 μ, usually about the size of a normal red blood cell, 7.5 μ.	Deeply staining, relatively large nucleus occupying most of the cell. Faint ring of non-granular protoplasm. Contains, rarely, basophilic granules. Neither ameboid nor phagocytic. The larger of these cells cannot be differentiated from the hyaline cell. Lobulation or polymorphism of the nucleus rarely present.
11 to 15 μ.	Faintly staining, relatively large, round, oval, notched or reniform nucleus, slightly larger than above. Broader ring of hyaline, faintly pinkish, grayish or light blue, non-granular protoplasm. Actively ameboid and phagocytic. Nucleus sometimes surrounded by faint rim of hyaline protoplasm, outside of which basophilic granules may be present. (This reaction best brought out by eosin and methylene blue).
7.5 to 11 μ.	This cell is also known as the polymorphonuclear leucocyte or polymorphonuclear neutrophile. It is sometimes called the polynuclear leucocyte. Irregularly staining nucleus; the nucleus is irregular, lobulated, reniform and not uncommonly like the figure 3, 5 or 7, or it may resemble the letter s, z or u. The nucleus may be apparently divided into three, five or even six parts, commonly connected by "underground" bands of chromatin; inability to demonstrate connection between the different parts of the nucleus led to the supposition that the cell was multi- or polynucleated. Irregularity in the contour of the nucleus is probably due to its being dried and fixed while still manifesting ameboid activity. The nucleus is rich in chromatin bands which may form a recognizable network in its interior. Protoplasm finely granular. The granules believed to be neutrophile are now regarded as faintly oxyphile or acidophile. The granules are commonly recognized over as well as around the nucleus. The cell is actively motile and phagocytic. Mitotic and amitotic division of the cells is sometimes demonstrable. These cells are sometimes regarded as the adult leucocytes of the blood. They are the most important if not the only pus cell. Sometimes cells are seen in the blood partaking of the characteristics of both the mononuclear and faintly oxyphile types; such cells are sometimes spoken of as transitional leucocytes.* * The writer is not kindly inclined toward the use of the word "transtional." The only excuse for its use is the fact that in enumerating leucocytes we occasionally come across cells which cannot be definitely placed. Reference has been made to this when considering the lymphocytes and hyaline cells between which we believe we recognize intermediate forms. Sufficient care in staining and careful focusing will usually, although not always, enable one to differentiate between these types.
Usually smaller than the preceding type. Diameter ranges between 7 and 10 μ.	Nucleus possessing many of the characteristics of the preceding variety. Rarely centrally placed. Chromatin network less conspicuous, often not recognizable; cells not uncommonly clearly polynuclear without recognizable connecting or "underground" chromatin bands between the different nuclei. Horseshoe-shaped and reniform nuclei frequent. Cell protoplasm not easily identified, with the exception of the granules, which are conspicuous even in the unstained cells. Granules large, clearly defined, highly refractile, usually discrete, but may be so abundant that differentiation is not easy. Take acid stains intensely. Stain reddish-brown with Ehrlich's stain. Actively ameboid, not usually believed to be phagocytic. Granules or matrix may contain bactericidal substances.
Relatively large; may exceed 20 μ.	Faintly staining, round or oval, structureless nucleus. Protoplasm usually difficult to demonstrate, may appear irregularly notched at the margin, granules slightly refractile in unstained specimens, large and abundant; stain deeply (purplish blue) with methylene blue or with the dahlia formula.
Rarely attains size of the finely granular oxyphile cell, usually much smaller.	Finely granular and coarsely granular cells are described by some writers as "mastzellen." Nucleus round or irregularly indented. Stains faintly, usually with less intensity than the granules, but of the same color. Granules like preceding variety, but very fine.
Usually 11 to 18 μ; average about 15 μ.	Pale, uniformly staining, eccentrically placed, ovoidal or round nucleus, resembling the hyaline cell. Protoplasm varies in quantity. The granules present in the protoplasm are usually not to be differentiated from the granules of the finely granular oxyphile cell. Stain reaction of the granules is not constant. Eosinophile granules and intermediate gradations of stain reaction occasionally present. Eosin and hematoxylin usually fail to demonstrate the presence of granules. Fixed by Flemming's solution, karyokinetic figures may be present. Probably identical with "cellules medullaries of Cornil." Cabot considers them intermediate between the hyaline cell and the finely granular oxyphile cell. While found in other diseases, it is in spleno-medullary leukemia that the presence of myelocytes assumes the most diagnostic importance.

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to the cubic millimeter, we shall find that not uncommonly the number of leukocytes will exceed this artificial boundary without there being, of necessity, any evidence of disease. On the other hand, if we adopt a standard above this point, or at least very much higher, we find that in certain well-recognized morbid conditions the associated leukocytosis falls within the artificial limit decided upon. It will thus be seen that it is quite impossible to draw a fixed line and to say that beyond this the accumulation of leukocytes is abnormal, while under this quantity the number is essentially normal. A standard of 10,000 to the cubic millimeter has been generally accepted as the maximum normal leukocytic count. There can be no objection to the figure, provided we understand that it is arbitrary and open to the objections just pointed out.

In a general way it may be said that leukocytosis may be physiologic or pathologic. The leukocytosis that follows digestion, the leukocytosis of the new-born, which not uncommonly persists until the end of the first year, and the leukocytosis at times associated with pregnancy are taken as examples of the so-called **physiologic leukocytosis.** Digestive leukocytosis is sometimes quite marked; thus, after a meal, particularly a meal rich in proteid food, the number of leukocytes may approach 50,000. The cellular elements in excess are the lymphocytes and finely granular oxyphile cells; sometimes the increase is more marked in one than in the other. This point is of value, as a blood examination made during digestion might, as a result of the large lymphocytic count, lead to erroneous conclusions, and the finding of an excess of finely granular oxyphile cells might also mislead. When gastric digestion is deficient or greatly delayed, it occasionally happens that there is no digestive leukocytosis, and, hence, the absence of digestive leukocytosis is not uncommonly regarded as an evidence of gastric disorder.

Inflammatory Leukocytosis.—This form is most frequently associated with suppurative, septic, or other inflammatory processes, and hence is occasionally referred to as **phagocytosis.** The term is misleading, as the same word is used in an entirely different sense. This form of leukocytosis is not uncommonly preceded by a brief stage of leukopenia, the extent and duration of which depend upon the promptness with which the body tissues react, and also on the virulence of the infecting factor. The prompt occurrence of this form of leukocytosis in acute infective disorders—such as pneumonia, acute bacterial conditions affecting serous membranes, streptococcal and staphylococcal infections, scarlet fever, and allied conditions—is taken as a favorable

omen; the occurrence of a leukopenia that persists is held to be an evidence of weak resistance or of overwhelming infection. Not uncommonly the count in inflammatory leukocytosis may approach 35,000, 40,000, or 50,000, and in rare instances the number of leukocytes present may be considerably greater. The leukocyte most abundant in this condition is the finely granular oxyphile cell. The large numbers of these cells present in the blood may so alter the percentage that repeated accurate observations may show that from ninety to ninety-five per cent. of the leukocytes are of this type. In some cases there is an increase in the number of lymphocytes and hyaline cells. As in other forms of leukocytosis, various opinions have been held as to the source of the added leukocytes and the essential etiology of the condition. It has been held that the leukocytosis is the result of nothing more or less than altered distribution; the finely granular oxyphile cells leaving the celomic cavities and entering the blood in response to infection. While it is not improbable that such a cause may be active, the large number of leukocytes destroyed at the point of infection,—as, for example, in abscess formation,—and the evidence of increased leukolysis, as shown by the excretions, point to the occurrence of increased leukocytic production.

The leukocytosis of malignant disease, syphilis, rickets, and the leukocytosis following hemorrhage, as well as the leukocytosis that not uncommonly precedes death (agonal leukocytosis), are by some writers grouped with the inflammatory increase of leukocytes. The leukocytosis observed in connection with malignant disease usually consists of an increase in the mononucleated forms of leukocytes (lymphoid and hyaline cells); the same is true of rickets, syphilis, and agonal leukocytosis, while leukocytosis following hemorrhage is usually of the finely granular oxyphile type.

Leukocytosis is usually more marked in the presence of sarcoma than in carcinoma, and is particularly evident when the former disease attacks the lymphatic structures.

Hemocytolysis.—Dissolution of the red blood-cell with liberation of the hemoglobin and endoglobular changes in the cell cytoplasm not infrequently occur in a sufficiently marked form to deserve consideration as a distinct pathologic process. Blood destruction is, in a sense, a normal process. The liberated blood coloring-matter resulting from cell dissolution is converted, in the liver, into bile pigment, and possibly enters into other normal chemic processes. When the process exceeds the normal or when cell destruction assumes an abnormal type, the resulting condition is spoken of as **hemocytolysis, hemoglobinemia,** or

by some writers as **hemolysis.** In the condition under consideration the cell elements primarily involved are the erythrocytes; when the cell destruction involves both red cells and leukocytes (erythrocytolysis and leukolysis), the term hemolysis is more appropriate.

Of the many causes presumed to be active in the production of hemocytolysis, no one satisfactorily explains the occurrence of the manifestation under all circumstances. When foreign blood is introduced into the circulation of an animal, and particularly when such blood is from an animal of another species, the added hemal cells promptly undergo fragmentation. The introduction into the circulation of large quantities of fluid may give rise to destruction of normal erythrocytes. Hemocytolysis occurs in connection with certain infectious diseases, among which may be mentioned smallpox, scarlet fever, diphtheria, enteric fever, and, possibly, to a varying extent, all the acute exanthemata. Bacteria and bacterial products circulating in the blood, as in septicemia and pyemia, may bring about the change. Malaria always induces more or less blood destruction, and in certain forms the process assumes grave proportions. Many poisons induce a similar change, and hemolysis arising from such causes is called toxic. A long list of poisons possessing the power might be given, the most important of which would be chlorate of potash, arseniureted and phosphoreted hydrogen, carbolic acid, pyrogallic acid, and various coal-tar derivatives other than those mentioned, such as anilin, antifebrin, antipyrin, etc. The blood destruction associated with poisoning by various fungi, and, indeed, the destruction associated with the introduction of venom, might properly be grouped with this class. Extremes of temperature seem to be influential in the production of this condition, and local tissue destruction from burns or frost-bites may bring about the change. The condition is sometimes associated with Raynaud's disease. A form of hemocytolysis is clinically recognized as **paroxysmal hemoglobinuria.**

Whatever may be the cause of the cell dissolution, liberated hemoglobin may be excreted by the kidney (hemoglobinuria) as methemoglobin or oxyhemoglobin, or the latter may be converted into the former by more or less prolonged retention within the bladder, and a sufficiently long stay in this organ may lead to the final conversion of oxyhemoglobin into acid hematin. An examination of the blood usually shows that it is dark in color, and the serum secured by coagulation or by the centrifuge may show a hemoglobin tint. Blister serum obtained from the patient may show the spectroscopic lines of free hemoglobin.

There is usually a marked reduction in the number of erythrocytes, associated with the presence of degenerating, fragmenting cells, chlorocytes, and achromocytes. Poikilocytosis, microcytosis, and megalocytosis are present to a varying degree. The reduction in hemoglobin may be marked. As a rule, there is little change in the number of leukocytes, although evidence of leukolysis may be present. The liver may be unequal to the task of removing the large quantity of hemoglobin, even with the occurrence of polycholia. The liver cells may show granular change and bile-staining; free pigment is not uncommonly present in the hepatic tissues. No constant renal lesion is demonstrable, although the kidney shows, for the most part, considerable staining, and the secreting substance may be brown or brownish-red in color; granular, desquamative, and other degenerative changes may be seen in the renal epithelium in marked cases, and free pigment may be present in the tubules; the Malpighian tufts are said to escape the deposit. Mention has already been made of the hemoglobinuria. Hemoglobin infarcts occur in the kidneys, and infarction is occasionally present in other organs.

Regeneration of the Blood.—After extensive hemorrhage, and from other causes, direct loss and blood destruction may reduce the number of red cells to 1,000,000 or less. Usually, with the subsidence of the cause regenerative processes rapidly ensue. After the loss of blood a temporary hydremia is brought about by the abstraction of fluid from the tissues. It is not improbable that the temporary hydremia, so induced, alters the specific gravity of the plasma and favors the actual solution of erythrocytes. Favorable to this view is the fact that chlorocytes and achromocytes, as well as fragmenting erythrocytes, may be found in the blood. Later, the mean diameter of the erythrocytes falls, and normoblasts are present in varying quantities. The fall in hemoglobin is at first proportional to the reduction in the number of red blood-cells, but later the color-index drops, and may fall as low as 0.5. During the process of erythrocytic regeneration nucleated cells may appear in varying numbers. The erythrocytes increase more rapidly than the hemoglobin, and, hence, the color-index remains low.

With the occurrence of hemorrhage a rise in leukocytic count is found. The leukocytosis rarely exceeds 25,000; in some cases it is absent. The white cell proportionately increased is the finely granular oxyphile. The length of time necessary for complete regeneration of the blood varies with the recuperative and hematogenic power of the individual and with the extent of

the hemorrhage. Repeated hemorrhage weakens the regenerative powers more rapidly and to a greater extent than a single copious hemorrhage. Attempts to establish a definite period within which hemal regeneration will occur are not well founded, by reason of the uncertainty in hematopoiesis in different individuals.

Anemia.—The term anemia has been variously defined, but, so far as a definition goes, nothing better has been offered than to call it "a poverty of the blood." In certain classes of cases the anemia is apparently dependent upon defects of the blood-making or blood-destroying organs, or, possibly, it would be better to say faults of hematogenesis or hemolysis, or both. Anemias in which no sufficient cause can be recognized in the organs or tissues are commonly referred to as **primary anemias.** In another class of anemias the blood condition is dependent upon some more or less evident lesion. These are the so-called **secondary anemias.** As our knowledge of pathology progresses we will, no doubt, class as secondary some of the anemias now regarded as primary. When we have demonstrated the factors influential in the production of an anemia, it becomes secondary to its demonstrated cause.

Secondary Anemia.—It is proposed to consider with this class those anemias in which it is possible to demonstrate a cause believed to be a sufficient explanation of the recognized change. As blood production is dependent largely upon the general nutrition and health of the individual, as well as upon the hematogenic functions, properly so called, it becomes evident that a large number of etiologic factors, often not even remotely associated, can be classed with the causes of symptomatic anemia. Unsanitary surroundings; improper, poor, or scanty food; overwork with insufficient food; emotional conditions influencing the appetite, sleep, etc., may all possess a varying importance in the production of anemia. Hemorrhage, copious and single, or scanty and repeated, may also be a cause. Painful affections, by reason of their influence upon the primary and secondary assimilation, may also favor the occurrence of an anemia. Intestinal parasites —such as anchylostoma duodenale and bothriocephalus latus— may induce anemia by interfering with the digestive process, by inducing hemorrhage, and possibly by elaborating some absorbable poison that influences unfavorably blood production or destruction. Anemia may depend upon the presence of parasites within the blood; the most conspicuous of these is the organism of malaria.

Acute infectious diseases commonly impoverish the blood.

During the activity of such processes the anemia may not be conspicuous, but with convalescence it not uncommonly becomes evident. With this group should be classed anemias following typhoid fever, scarlet fever, smallpox, etc. So-called chronic infectious diseases are also associated with the occurrence of anemia, which may of itself be a striking symptom; the anemias of syphilis and tuberculosis are most typical. The anemia of scurvy and purpura should be mentioned. Certain of the secondary anemias are called toxic, and are dependent upon poisoning by lead, arsenic, phosphorus, mercury, etc. Malignant tumors (carcinoma and sarcoma) usually give rise to a form of anemia that may constitute an important factor in the diagnosis of such conditions.

Diseases of various organs influencing the general nutrition are not uncommonly associated with anemia. The anemias of chronic nephritis, of heart disease, and of chronic intestinal inflammations belong to this group.

The Conditions in Secondary Anemia.—The table on pages 448 and 449 gives in a general way the blood changes in this condition. It is probable that the disease ordinarily referred to as simple anemia is truly an example of secondary anemia, and that it should be considered with this group. It will be observed that the blood changes in secondary anemia possess nothing characteristic, and depend more upon the intensity of the anemia than upon any other factor. The reduction in red blood-cells varies within wide limits. A fairly evident secondary anemia may show a blood count of 4,500,000, while, at the other extreme, a count below 1,000,000 may occur. The corpuscular changes also depend upon the extent of the anemia. It may be said that in the milder anemias there is little distortion of the erythrocytes, and but few abnormal cells are present. In more marked anemias poikilocytosis and microcythemia occur, while in the graver forms megalocytosis and nucleated erythrocytes are found; megaloblasts are rare; normoblasts are more abundant. Polychromatophilia (abnormal stain reaction) is usually proportionate to the degree of the anemia.

The hemoglobin always shows greater reduction than the corpuscular count would justify (low color-index), and may not exceed twenty per cent. The leukocytes are but little, if at all, influenced by the mere occurrence of secondary anemia. The condition that produced the anemia may determine a leukocytosis the character of which will depend upon the cause. It is usually stated that when the blood counts are low, a leukocytosis is likely to be present; this is not, however, an invariable rule.

The visceral lesions associated with this form are dependent upon the cause and upon the extent of malnutrition. Granular changes occur in glandular viscera, notably the kidney and liver. A similar change is seen in the heart. Degenerative changes in the capillary system are indicated by the concomitant edema. The degenerative lesions are probably dependent upon overwork of the organs involved, associated with poor nutrition, and possibly to a limited extent upon the toxic effects of poisons generated within the blood or arising from other causes and acting themselves as causes of the existing anemia.

CHLOROSIS.

Synonyms.—Febris Amatoria; Greensickness; Morbus Virgineus; Chloremia; Chloranemia; Bleichsucht (German).

Chlorosis is primarily a disease of young women, marked by more or less reduction in the number of erythrocytes and still more evident oligochromemia.

Causes.—As just stated, the disease is practically restricted to women, and is most frequent between the ages of fourteen and eighteen years, although it occasionally appears later in life (*chlorosis tarda*). A condition closely resembling chlorosis is sometimes seen in men. A family history of tuberculosis, faulty hematogenic power, or heredity, as indicated by cases appearing in successive generations, may be predisposing factors. Emotions, such as grief, fear, anxiety, homesickness, and disappointed love, have been regarded as causes. Hypoplasia of the heart and greater vessels, and sometimes of the generative organs, has been observed. Autointoxication, constipation, menstrual disturbances, unsanitary surroundings, overwork, and faulty or insufficient diet may cause or predispose toward the condition. Hemorrhage, as by epistaxis, menorrhagia, and bleeding from hemorrhoids, intestines, or stomach, are often assigned as etiologic factors. Race and climate, particularly among civilized nations, seem to have no influence upon the occurrence of this malady. Lloyd Jones believes that the disease is more common in girls belonging to large families, and that it not uncommonly constitutes part of a general condition one of whose manifestations is unusual fertility. Dyspepsia and constipation associated with the disease are generally not regarded as etiologic factors, although one of the toxic theories (autointoxication) is based upon the belief that the blood condition is due to copremia or some allied state. In the present state of our knowledge infectious theories are not to be regarded with favor.

Blood Changes.—The blood is easily obtained, flows freely, and is usually bright red in color. The specific gravity of the serum is normal or higher than normal, while the diminished hemoglobin gives an unusually low (1030) total specific gravity. Alkalinity seems to be increased. There is an oligocythemia that varies within wide limits, and is not commonly marked. The oligochromemia is usually the most evident change. In mild cases the erythrocytes fall to eighty per cent. of the normal and the hemoglobin to fifty per cent.; in more marked instances the erythrocytes approach fifty per cent. of the normal and the hemoglobin thirty per cent. or less. Hayem has reported a case in which the red blood-cells fell to twenty per cent. and the hemoglobin to sixteen per cent. It will thus be seen that the reduction in hemoglobin is always greater than the corpuscular reduction (low color-index). In about forty per cent. of the cases the number of red blood-cells does not fall below 4,000,000. The erythrocytes show a mean reduction in diameter, and are strikingly pale. Microcythemia, poikilocytosis, and polychromatophilia are present to a varying extent. Nucleated red cells are rarely abundant, although occasionally a few normoblasts occur. The presence of macroblasts is usually regarded as an unfavorable sign. The platelets are slightly increased. There may be no important change in the leukocytes, with the exception of the occasional occurrence of myelocytes. While it is commonly stated that these cells are absent, there can be no doubt of their occasional presence in grave cases. (See table, pp. 448 and 449.)

Associated Lesions.—The panniculus adiposus is usually abundant, and the general nutrition, aside from the pallor, seems fair or even good. The pallor of all the tissues may be striking. Granular and fatty changes occur in the heart, and aortitis is occasionally present. Hypoplasia of the heart and aorta has already been mentioned. Fatty changes in the capillary, renal, and gastric cells have been noted. In spite of the fact that the blood coagulates less rapidly than normal outside the vessels, venous and capillary thrombosis and thrombosis within the cranial sinuses may constitute important lesions during life. The morbid anatomy and blood changes fail to explain the peculiar venous hum observed during life. Changes in venous caliber, and in the blood itself, as causes of this important phenomenon deserve mention, although the demonstration is by no means satisfactory.

PERNICIOUS ANEMIA.

Synonyms.—Addison's Causeless Anemia; Idiopathic Anemia; Essential Anemia; Progressive Pernicious Anemia; Myelogenic Anemia; Ganglionic Anemia; Anæmatosis; Biermer's Disease.

Pernicious anemia is a morbid condition associated with excessive hemolysis and inadequate hematogenesis (West), and for which no sufficient cause has been demonstrated. While an adequate cause has not been recognized, certain predisposing elements are regarded as important factors in the production of disease; of these predisposing causes the following may be mentioned: pregnancy, parturition, starvation, hemorrhage, degeneration of the mucous membranes of the alimentary canal. The disease is more frequent in adults, although cases in children have been reported.

Blood Changes.—The blood is often difficult to obtain, pale, and watery, although occasionally it assumes a coffee or chocolate color. A drop forming at the point of puncture is usually not rounded and elevated, as normal, but flattened, and may spread over adjacent surfaces. Oligocythemia is marked; blood counts below 1,000,000 are not infrequent, while a count as low as 143,000 has been reported by Quincke. Occasionally, blood counts may, for a time, approach the normal, rising to or exceeding 5,000,000, followed by relapse and death. The average size of the erythrocyte is increased, and may approximate 9 μ. The large cells (megaloblasts), which markedly increase the mean diameter of the erythrocytes, may constitute from three to twelve per cent. of the red cells. Megalocytes possessing diameters between 10 μ and 16 μ occur. Microcytes are not, as a rule, abundant. Nucleated red cells are usually, but not constantly, present. So-called crises occur in which an unusually large number of normoblasts may be thrown into the circulation, followed by an increase in the number of red cells. Free nuclei are sometimes present in the blood, and occasionally one sees a nucleus with shredded protoplasm containing hemoglobin, attached to its periphery. Both normal and abnormal sized red cells may show polychromatic reactions. The presence of unusually large nucleated cells (megaloblasts) is regarded as unfavorable. By reason of the irregularities in the size and contour of the erythrocytes, rouleaux formation is peculiar. Oligochromemia does not approach in extent the oligocythemia. The relatively high color-index is usually held to depend upon the large number of red cells the diameter of which exceeds that of the normal cell; and as the more marked the anemia, the more abundant such cells

become, it is commonly found that the fall in corpuscles is not associated with a corresponding fall in hemoglobin, and that the corpuscular count may be ten per cent. of the normal or less, and the hemoglobin from fifteen to twenty per cent. of the normal or more. The specific gravity of the total blood is decreased; the platelets are said to be increased, and occasionally show peculiar and excessive agglutination. No change especially worthy of note regarding the leukocytes occurs, with the exception of the usual presence of myelocytes. These are not abundant, and rarely exceed two or three per cent. of all the leukocytes. There is sometimes a slight increase in the number of lymphocytes, and occasionally a proportionate diminution in the number of finely granular oxyphile cells. Leukolysis and tinting of the protoplasm of the white cells by hemoglobin may be recognized in some cases. (See table, pp. 448 and 449.)

Associated Lesions.—In spite of the extreme anemia, emaciation is not present. The skin is pale, but may show a faint icterus; the peculiar lemon hue may be manifest in the conjunctiva. Petechiæ are occasionally present. There is not uncommonly a small amount of edema, particularly on the lower extremities. The panniculus adiposus may be abundant; it is usually yellowish in color, contrasting strongly with the red muscles. Coagulation of the blood in the great vessels and in the heart may be delayed or absent. The presence of free hemoglobin in the blood serum and in the serous fluids may be marked and may be sufficient to stain the hands. Fatty and granular changes occur in the heart. Similar degenerative processes are occasionally seen in the arteries and capillary walls. Atrophy of the gastric mucosa has been described. The spleen and kidneys may show pigmentation. Tracings of sclerosis have been described in the central nervous system. The bone-marrow usually shows reversion to the fetal state, and contains a large number of nucleated hemoglobin-containing cells (erythroblasts); the larger cells may show evidence of phagocytic power. The liver is usually enlarged and may be fatty, and constantly contains an excess of iron. Normally, the percentage of iron is from 0.078 to 0.12, while in pernicious anemia it not uncommonly reaches 0.7. The iron is distributed in the hepatic cells at the periphery of the lobule, where it is usually abundant. (For demonstration of iron in tissues see p. 230.)

Occasionally, an excess of iron will be found deeper in the lobule, and at times the interlobular tissue may contain a trace.

It is generally conceded that, essentially, pernicious anemia is due to an excessive hemolysis. This is indicated by the

occurrence of disintegrated cells—microcytosis, polychromatophilia, plasmorrhexis, etc.; the hepatic changes offer additional support to this theory, and also indicate that the hemolysis occurs within the portal circulation. The large percentage of iron in the liver supports this view, and the absence of hemoglobinuria would indicate that the hemocytolysis did not occur in the general circulation.

LEUKEMIA.

Synonyms.—Leukocythemia; Lymphadenia.

In this disease there occurs a most marked increase in leukocytes, which, while it varies within wide limits, is usually a constant feature throughout the disease. Leukemia occurs in the lower animals, notably the cat, dog, ox, sheep, and hog.

Causes.—Leukemia may occur at any age. It is most frequent during middle life—thirty to fifty years. It is twice as frequent in man as in woman. A history of malaria is present in a certain percentage of cases. Injury to the spleen is sometimes followed by leukemia. Pregnancy, lactation, rickets, and syphilis sometimes antedate the appearance of symptoms. The scanty evidence of heredity does not favor the view that it is an important factor. Certain facts in the history of some cases would indicate the possibility of its being an infectious disorder, and while protozoa and various bacteria have been described as present in the blood in some cases, and while it is claimed that the disease has been communicated to lower animals, the evidence must be regarded—for the present, at least—as incomplete; experienced investigators have failed to demonstrate the presence of bacteria in the blood, and inoculation in animals has proved futile. By some the process is regarded as allied to tumor formation. This view would regard the blood as a tissue the intracellular substance of which is fluid, and the added cellular elements present in the blood would be considered tumor cells. The fact that the cells invade the organs, or at least are found infiltrating various organs and tissues, is adduced to support the theory. Nothing satisfactory in the way of demonstration has been given, and at best the view can be looked upon merely as a working hypothesis.

Theoretically, three forms of the disease are admittedly possible—*splenic*, *myelogenic*, and *lymphatic*. The coincident presence of the blood changes of two forms may give rise to what is usually considered as *mixed leukemia*. Clinically, but three forms are usually recognized—the *splenomedullary*, *lymphatic*, and *mixed*. With regard to time of invasion and duration, the

disease is said to be *acute* or *chronic*. The splenomedullary cases belong to the chronic type of the disease. Lymphatic leukemia usually runs a more acute course.

The Blood Condition.—When the number of leukocytes is large, the blood may be pale, and even slightly turbid, and marked oligocythemia, with associated reduction in blood coloring-matter, may give rise to a thin, watery consistence, and, as a result of the presence of a large number of leukocytes, a yellowish tint. The alkalinity is lowered. The statement that the blood is acid appears to be unsupported by facts. Coagulation is delayed, and this delay is most marked in the presence of marked oligocythemia and oligochromemia. The actual quantity of fibrin present is said to be increased. The two statements are reconciled by the belief that peptone is present, which, as is well known, delays coagulation.

Splenomedullary Leukemia (*Medullary or Myelogenic Leukemia or Leukocythemia; Myelemia; Myelocythemia*).—As a distinct marrow-form of the malady has not been shown to exist, and as it has not been established that the disease begins in the marrow, the term myelemia or myelocythemia with splenic engorgement is generally conceded not to be acceptable. The total number of leukocytes may approximate 500,000; usually, the count does not exceed 1,000,000 or 2,000,000, and at times may fall within normal limits. The enormous addition of myelocytes is the most conspicuous change in this form of the disease. These cells may constitute from twenty to fifty per cent. of the leukocytes present—a percentage never approached in any other form of leukocytosis. The smaller forms of myelocytes may manifest ameboid movement. There is a marked increase in the finely granular oxyphile leukocytes, although the preponderance of myelocytes materially alters the percentage. Instead of from sixty to seventy per cent. of the leukocytes belonging to this group, the percentage varies between ten and fifty. The uninuclear cells, the lymphoid and hyaline cells, are uninfluenced or are slightly diminished. Myelocytes showing karyokinesis are occasionally present.

The red cells are usually diminished in number; the extent, however, of the reduction varies in different cases, and more or less at different periods in the history of any given case. Sometimes the count may be normal; in other cases the oligocythemia may be most marked. Eichhorst has reported a case in which the red cells were reduced to 316,000 to the cubic millimeter. The reduction in red cells proportionately reduces the hemoglobin; marked alterations in the color-index are not un-

commonly present. A conspicuous morphologic change is the abundance of nucleated red cells. Normoblasts are rarely absent; microblasts and megaloblasts are never so abundant. Poikilocytosis is not commonly conspicuous. The blood platelets show no constant change, being sometimes diminished, sometimes increased. Charcot-Leyden crystals are occasionally seen. (See table, pp. 448 and 449.)

Lymphatic Leukemia (*Lymphocythemia; Lymphemia*).—Leukocytosis is not so marked as in splenomedullary leukemia. The proportion of leukocytes to red cells rarely exceeds 1 of the former to 12 or 20 of the latter, and the total count of leukocytes ranges between 40,000 and 400,000, rarely exceeding 200,000 or 250,000. The leukocytes most abundant in this form are the uninuclear cells; in some cases the lymphocyte predominates; in other cases the hyaline cell. The finely granular oxyphile cells are diminished, and the coarsely granular oxyphile cells are scanty or absent. Myelocytes, if present, are never abundant. Oligocythemia is more conspicuous and constant in this form of leukemia. The count of the red cells may show from 1,000,000 to 2,000,000. Abnormal forms of red cells are less frequent in this form of leukemia, although they are occasionally present. (See table, pp. 448 and 449.)

Mixed forms of leukemia partake of the blood changes of both forms described, and do not here merit special consideration.

The names given to the different forms of leukemia are not based upon changes in the organs; enlargement of the lymphatic glands is not a constant feature of lymphatic leukemia. Changes in the organs usually depend upon the duration of the disease rather than upon the character of the blood-cells, being more marked in chronic cases.

The spleen may be greatly enlarged, weighing as much as eight kilograms. The capsule may be fibrous or even cartilaginous. The shape of the organ is not altered. Infarcts may be recognized upon the surface or on section. Associated infectious processes produce less softening in the leukemic organ than in the normal spleen. The color of the pulp is further influenced by the number of red blood-cells, and as leukemic patients are prone to hemorrhage, a pinkish or pale pulp may be induced thereby. In the absence of such condition the pulp is usually redder than normal. In a uniformly red organ the Malpighian bodies may not be recognizable. The extensive intercalation of leukocytes may, even in the paler pulp, obscure the Malpighian bodies. As already stated, the density of the organ is more

marked in the chronic form of the disease. Under the microscope the splenic reticulum may show some increase, although it is not commonly much in excess of the normal. Occasionally, it shows more or less hyaline change. The most striking feature is the abundance of leukocytes. These are usually of the form in excess in the blood. The more chronic the case and the greater the splenic enlargement, the more marked the leukocytic intercalation.

The changes seen in the bone-marrow usually assume one of two types, although intermediate grades are occasionally noted. Both of these types have received inappropriate names. *Pyoid marrow* is yellowish in color and soft in consistence. The marrow usually present is firm, pink or pinkish-gray in color, and is called *adenoid* or *lymphoid marrow*. The abnormal marrow displaces the fatty marrow of the long bones. Histologic changes of the splenomedullary form consist of an enormous increase in the number of normal marrow-cells. Erythroblasts, normal in size, and cells of the larger and smaller types, are usually found; large phagocytic marrow-cells are present. Evident cell proliferation is not uncommonly present, and in a few cases has been conspicuous. The gross appearance of the marrow in lymphatic leukemia does not differ from that observed in the splenomedullary form. The leukocytes present are, however, of the hyaline and lymphocytic types—normal marrow-cells being displaced by the lymphoid infiltration.

Lymphatic Glands.—In nearly all cases of lymphatic leukemia enlargement of these glands occurs at some time or other in the progress of the disease. In some cases the enlargement is restricted to an anatomic group; in other cases different areas may be involved; and still less frequently the condition may be general. On section, the glands are pink or grayish-pink in color, soft, and juicy. Confluence is not common, and even where a large group of glands has apparently merged into a single mass, differentiation of the nodules may be possible. The enlargement of the gland seems to be due to engorgement of its channels, including the peripheral sinuses. In the less frequent glandular enlargement of the splenomedullary form the lymphatic sinuses are distended by leukocytes presumably coming from the blood.

The Liver.—The organ usually shows considerable enlargement, and may weigh as much as six kilograms. It is commonly pale, and the pallor may be most conspicuous along the course of the portal channels. The extreme pallor is frequently due to the intercalation of leukocytes, the distribution of which may be patchy, local, or general.

The kidneys may be enlarged, and lymphoid intercalation may be marked.

Increase in the lymphoid tissue is always noticed in the thymus and lymphoid elements of the alimentary canal, as well as in the lungs, and even in the skin. The tendency toward hemorrhage, previously remarked upon as a clinical phenomenon, is further shown by the occurrence of visceral hemorrhage and of hemorrhage into the newly formed areas of lymphoid tissue, into the joints, and even into the brain.

No satisfactory explanation has been offered for the increase in leukocytes and the associated intercalation of these cells in the various organs. It has been held that the leukocytic increase is dependent upon proliferation of the lymphoid tissue from which leukocytes are thrown into the general circulation. It has also been maintained that the lymphocytic infiltration of the various organs and tissues represents the accumulation of leukocytes deposited from the blood. White and Hopkins favor the belief that the increase in leukocytes is dependent upon diminished destruction of the cells.

Pseudoleukemia (*Hodgkin's Disease*).—This morbid condition resembles leukemia in its anatomy, but differs materially in the character of the blood changes. Like leukemia, it may assume a chronic as well as an acute form, and, like leukemia, splenic enlargement may predominate over the changes in the lymphatic glands.

Splenic anemia—sometimes called *pseudoleukemia splenica*—is regarded by some as a splenic form of Hodgkin's disease analogous to the splenomedullary form of leukemia. The changes in the blood in leukemia and in splenic anemia, and their differentiation from leukocythemia, will be found in the accompanying table. (See pp. 448 and 449.) For further consideration of the morbid anatomy of Hodgkin's disease see Diseases of the Lymph-glands.

Mycoses of the Blood (see Intoxications and Infections, pp. 385 and 389).—The possible infections of the blood may be greater than is at present believed. The organisms of anthrax, tuberculosis, glanders, typhoid fever, and relapsing fever, also the pyogenic and a few other bacteria, have been identified in the blood. Care must be used in drawing conclusions from the presence of bacteria in the blood postmortem, as it has been satisfactorily demonstrated that in the agonal period—the final moments or, it may be, hours of the death agony—bacterial diffusion is favored by the lessening bactericidal action of the blood and the probable increasing permeability of the vessel walls. The demonstra-

tion of bacteria in the blood does not materially differ from their demonstration elsewhere. Trustworthy conclusions are rarely possible from an examination of a drop of blood obtained by simply pricking the skin, as already directed. The method of Sittmann is to be commended. A vein, preferably one in the arm, is exposed under the most rigid aseptic methods,—previous sterilization of the skin, instruments, operator's hands, etc.,—and a sterile cannula is thrust into the vessel, which may be caused to distend by proximal obstruction, as by pressure by the finger or a fillet applied above the point elected for opening. The blood flowing from the cannula is received in a sterile container (flask or test-tube sterilized by heat), and the subsequent examination is conducted upon principles laid down in chapter III, part I.

Animal Parasites.—The animal parasites found in the blood are broadly classed as hematozoa. The most important are the malarial organism (p. 211), the embryo of the filaria sanguinis hominis (p. 199), and the distoma hæmatobium (p. 196). The last named is really a parasite of certain vessels—the portal vein and its branches and the venous ramifications around the bladder and rectum. (See Animal Parasites.)

	DISEASES.	GROSS APPEARANCE AND SP.GR.	HEMOGLOBIN AND COLOR INDEX.	NUMBER OF ERYTHROCYTES.	SIZE OF, AND FORM CHANGES IN RED CELLS.
PRIMARY ANEMIAS.	CHLOROSIS.	Blood flows readily. Pale red watery Extravascular coagulation slow; intravascular, frequent. Sp. gr. of total blood decreased. Sp. gr. of plasma slightly increased.	Greatly reduced. Color index constantly low.	Normal or slightly reduced.	Decreased in size. Poikilocytosis only in severe cases, and rarely marked.
	PERNICIOUS ANEMIA.	Blood flows scantily, often difficult to obtain. Watery, pale red (often coffee color). Coagulation slow. Sp. gr. decreased.	Marked reduction. Color index usually high.	Pronounced oligocythemia. Rouleaux formation scanty or absent.	Marked variation in size. Macrocytes predominate. Poikilocytosis more marked than in any other anemia.
	SIMPLE PRIMARY* ANEMIA.	Paler red than normal. Coagulation slightly more rapid. Sp. gr. decreased.	Moderate reduction. Color index normal or nearly so.	Moderately diminished.	Normal or slightly decreased in size.
	LEUKEMIA. SPLENO-MEDULLARY LEUKEMIA.	Light red or milky Less fluid, coagulation slow. Sp.gr. decreased. Alkilinity usually diminished.	Slightly reduced. Color index below normal.	Usually only a slight reduction.	A slight reduction; poikilocytosis slight.
	LYMPHATIC LEUKEMIA.	Resembles Spleno-medullary type, except that changes are not so pronounced. Alkilinity usually diminished.	Reduction more marked than in Spleno-medullary type. Color index low.	Reduced. Always more pronounced than in Spleno-medullary type.	Reduction in size, and distortion more striking than in splenomedullary type.
	PSEUDO-LEUKEMIA OR HODGKIN'S DISEASE.	Paler red than normal, depending on severity. Coagulation more rapid. Sp. gr. normal or slightly decreased.	Reduced, depending on severity and stage. Color index normal or lower.	Diminished, depending on severity and stage.	May be undersized. Poikilocytosis in severe cases.
	SPLENIC* ANEMIA.	Pale red, more watery. Coagulation more rapid. Sp. gr. decreased.	Reduced. Color index normal or lower.	Reduced, sometimes to one-fourth of normal.	Normal; usually slightly reduced. Poikilocytosis seldom excessive.
	SECONDARY ANEMIAS.	Pale red, depending on severity; watery. Coagulation usually rapid. Sp. gr. decreased	Reduction varies, depending on severity. Color index usually below normal.	Diminution varies with condition.	Usually decreased. Poikilocytosis in a number of severe conditions.

* By some authors not recognized as a primary anemia.

CHANGES IN ANEMIAS.

Nucleated Red Cells.	Number of Leucocytes.	Lymphocytes and Hyaline Cells.	Finely Granular Oxyphile Leucocytes.	Myelocytes.	Blood Plates.
Rarely found. Normoblasts are present in severe cases.	Generally normal.	Occasionally relatively increased.	Normal or relatively diminished.	Rarely found.	Increased.
Microblasts, normoblasts and megaloblasts present. The latter most numerous.	A moderate leucopenia may be present.	Usually relatively increased.	Commonly decreased, relatively.	Small number nearly always found.	Diminished.
Only in severe cases.	Generally normal.	Sometimes increased relatively.	Sometimes decreased relatively.	Absent or rare.	Increased.
More frequent than in any other form of anemia. Normoblasts predominate.	Enormous increase. In no other anemia are leucocytes so abundant.	Increased, but relatively diminished	Increased, but relatively diminished.	Myelocytes form a large percentage of the leucocytes, often 60%. (Basophilic cells included.)	Increased.
Rarely present	Greatly increased, but not to the extent found In the Spleno-medullary type.	Greatly increased (as high as 90 per cent. or more. Sometimes small and other times large are increased	Relatively decreased.	Absent or rare.	
Usually absent. May be present when disease is marked.	Normal or slightly increased.	Generally normal.	Generally normal.	Rarely found.	Increased.
Rarely present.	Normal or slightly increased.	Generally normal. Usually increased if fever is present.	Generally normal.	Rarely found.	Increased.
Rarely met with in mild anemias, but not uncommon in pronounced cases.	Generally increased. Seldom normal or decreased.	Usually diminished.	Usually increased.	May be found in some cases.	Usually increased.

CHAPTER II.

SPLEEN.

The **spleen**, in the course of the postmortem, is the first organ examined in the abdominal cavity. It varies greatly in size and weight, usually weighing between 150 gm. and 350 gm., and measuring from 10 cm. to 15 cm. in length, 6 cm. to 10 cm. in breadth, and 2.5 cm. to 4 cm. in thickness; the relation to the weight of the body is about 1 to 360. The color varies considerably, even in health, and undergoes important changes after death; the same may be said of the consistency.

Postmortem Changes in the Spleen.—In the presence of any engorgement or necrotic process the spleen quickly undergoes postmortem disintegration. As a result of attachment to the stomach, digestion may give rise to disintegration of the gastric wall which may extend into the splenic tissue. Sulphureted hydrogen passing through the wall of any adjacent hollow viscus gives rise to precipitation of the iron present in the splenic tissue, as a result of which the organ shows *pseudomelanosis*, at first restricted to the area of contact, but in time, and particularly where decomposition is in progress, involving the whole surface of the organ. The layer of postmortem pigmentation is usually thin, rarely extending to a depth of one centimeter.

Emphysema of the spleen is usually held to be a postmortem process, and depends upon the evolution of gas in the splenic pulp as a result of infection by some gas-producing organism, such as the bacillus capsulatus aerogenes, colon bacillus, etc.

Malposition.—Splenoptosis, *wandering* or *movable spleen*, arises as a result of relaxation or stretching of its normal attachments. The extent of the displacement may be very marked, the viscus at times becoming a pelvic organ. It is probable that the lengthening of the suspensory ligament may be caused by an increase in the size of the spleen, and, most certainly, the organ displaced becomes larger, the increase in size being partly due to the obstruction to venous return, brought about by the tension on the splenic vein impeding the flow of blood on its way to the liver.

The condition is more common in women than in men, and is most frequent in women who have borne a number of children. Relaxation of the abdominal walls favors displacement of the

organ by partial withdrawal of its normal support. The splenic malposition is frequently but a part of the downward displacement of nearly all the abdominal viscera—a condition receiving the name *viscceroptosis, enteroptosis, splanchnoptosis, or Glénard's disease.* The spleen may be forced from its normal position by spinal curvature, tumors and swelling in the retrosplenic area, and assumes a lower level as a result of inflammatory effusion, morbid growths, etc., in the left pleura. The organ is sometimes pulled out of place by attachment to an adjacent prolapsed viscus, as the colon, stomach, kidney, or spleen. The long pedicle necessary for such marked displacement as is seen when the spleen is located in the pelvis or in the right iliac fossa is usually made up of the splenic artery and vein, with a certain amount of connective tissue, in which may be embedded a part of the pancreas. The danger in wandering spleen is twisting of the pedicle and obstruction to the blood supply of the displaced organ. Interference with the venous circulation may be brought about, slowly inducing congestion, with marked induration of the spleen (*cyanotic induration*). It is alleged that the interference with circulation may give rise to atrophy, although the author has never observed such a condition. When the obstruction, either venous or arterial, is complete, necrosis, which may be manifested as a general softening of the organ or as gangrene, occurs. The liability of wandering spleen to circulatory disturbance is further evinced by the fact that it not uncommonly contains infarcts; these may be of different ages. As a result of localized peritoneal inflammation and capsulitis, the wandering spleen may become attached in some abnormal position, and has been mistaken for a neoplasm arising at the point of attachment.

In addition to the wandering spleen, there is occasionally seen, as in the liver, a partial rotation of the organ on its long axis, thus presenting an edge for percussion and other physical examination, and misleading the clinician as to the size of the organ. In the *situs inversus* the organ is on the right side.

Malformation.—The spleen may be absent. *Hypoplasia* of the organ is more common. *Splenculi*, or *accessory spleens*, are quite frequent. The number of splenculi varies. Usually one or two are found. Instances have been reported, however, in which as many as forty accessory spleens were present. The accessory organs may be situated near the hilum of the normal organ, in the splenic pedicle, in some peritoneal fold adjacent to the spleen, or even upon the opposite side of the abdominal cavity. Rarely, they are found in the spleen itself, and are occasionally embedded in other organs, as the pancreas. Histologic-

ally, the structure of the accessory organs is identical with that of the normal spleen, the former being nothing more than miniature reproductions of the normal. They are probably physiologically accessory to the normal spleen, and may undergo hypertrophy after removal of the fully formed organ. It has usually been found that where animals show no disturbance of health as a result of splenectomy, accessory spleens have hypertrophied and have assumed the function of the organ removed.

Multiple Spleen.—Instead of a single organ approaching the normal, with a number of accessory spleens, there are sometimes found two or more smaller spleens of approximately the same size. Garrod has observed nine spleens in one cadaver. Multiple and accessory spleens are liable to the same diseases as the normal organ.

The normal splenic notch may in rare instances be absent, and in other cases a number of notches are found. Occasionally, the normal notches are deep, and practically amount to incisures or fissures, giving rise to the so-called *lobulated spleen.*

Atrophy of the spleen is said to occur. In the very old the organ is likely to be small. The typical *senile spleen* is usually small, with a wrinkled capsule, which may be considerably thickened. In the absence of any preceding or associated condition giving rise to pigmentation the organ is usually pale. The Malpighian bodies and splenic pulp are atrophied, and the fibrous septa are thickened. A closely allied, but by no means identical, condition is found in large spleens with atrophied Malpighian bodies and intensely hyperemic pulp. As a result of fibrous change, a certain amount of contraction may be present.

Hypertrophy of the Spleen.—Little is known of true hypertrophy of this organ. By some the enlargement of the spleen seen in splenic anemia, Hodgkin's disease, and leukemia is held to be an example of hypertrophy. The increase in size seen in malaria is surely not a true hypertrophy. With regard to the others, they will be considered more fully with the diseases in question.

Pigmentary Infiltration.—In chronic malaria the spleen may acquire an enormous size and be intensely pigmented. The viscus may weigh as much as five kilograms, or even more. During the earlier infections the spleen is soft, the pulp being almost diffluent and of a dark-brown chocolate color. Thrombosis of the smaller blood-vessels and areas of necrosis are not infrequently present. Later, or after repeated infections, the organ becomes greatly enlarged, firmer, cutting with considerable resistance, as a result of a decided increase in the fibrous tissue

("ague cake"). It may be of a dark slate-color, due to the contained pigment. Histologically, the fibrous septa, the trabeculæ, and the pulp will all show an abundant increase, with wide-spread deposit of melanin throughout the connective tissue and pulp. The parasite of malaria may be found in the spleen, and leukocytes containing the parasite are not infrequently present.

Lardaceous Disease.—The spleen is large, and may be voluminous, weighing five kilograms; it is lighter in color and of high specific gravity, with deposits of amyloid material in sago-grain-like bodies; hence the name, *sago-spleen*. The iodin reaction renders its recognition clear. (See Lardaceous Disease, p. 228.) Under the microscope the amyloid material will be seen to occupy the Malpighian bodies; in the earliest stage it probably occurs as an involvement of the arterial branch that the Malpighian body surrounds. There is a form of amyloid spleen in which the infiltration is more diffuse, not in the distinct sago grains, as just described, but involving the pulp and fibrous septa. The chemic reaction is equally well marked, but is more diffuse and less punctiform than in the sago-spleen. (See Plate I.) As already described, amyloid disease arises in a number of organs almost simultaneously, but the spleen seems to suffer most in the early stage of a wide-spread morbid condition, and, for this reason, any large, rather pale organ should be carefully tested with iodin to differentiate clearly between the enlargements, due, for example, to leukemia, and those of amyloid disease. The occasional deposit of hyaline material in the septa, vascular twigs, and reticulum has been regarded as a form of degeneration. It is possibly but a step in the evolution of lardacein.

Calcareous infiltration is seen in the spleen as a result of past necroses, inflammations, or chronic infections. Lime salts are not infrequently deposited in the thickened capsule of chronic capsulitis, which may extend over a considerable area and assume a bony or stone-like hardness. The periphery of quiescent tubercular areas, cyst-walls, and the cicatrices of old infarcts may show calcareous infiltration.

Splenic Engorgement.—In acute sepsis, and in many of the acute infectious diseases with bacteria or their products circulating in the blood, the spleen seems to become distended with blood; its pulp grows soft and diffluent, and the whole organ becomes edematous and enlarged. This has been considered an *acute engorgement*,—an *acute hyperplasia* of the organ,—the result of the accumulation of broken-down elements, and by some a reactionary phenomenon by which the spleen, accessory to other organs, is enlarged in an effort to elaborate a power—to

be manifested through the leukocytes or antitoxins, or in some other way—which may successfully combat the noxious agents circulating in the blood. As we are not fully aware of the functions of the spleen or of the organs at work in resistance to infections, the precise cause and process can not, for the present, be definitely explained.

In addition to the gross changes previously noted, the tension of the capsule may be striking, and during life it may be so great that, with the softening, the spleen may rupture. Postmortem, such an organ is rarely removed without a tear in its capsule through which the abnormally dark, grumous pulp is easily squeezed out. Such an organ will show, under the microscope, a pulp distended with blood, an enormous number of leukocytes, and the red cells advancedly fragmented. If bacteria are circulating in the blood, the splenic interstices may be distended by the invaders. The pulp-cells may be found in all stages of their life history—karyokinetic, active, cloudy, granular, and fragmenting; the displaced and softened fibrous network manifests the separation of fibers incident to edema and vascular distention. Commonly, the splenic pulp contains a large number of phagocytes in which may be found bacteria. That the condition is not always an infection is shown by the fact that it can be produced by abrin, ricin, and by large doses of nitrate of sodium. These considerations, with other clinical and experimental data at hand, would lead us to regard the change as depending upon a toxemia. That all toxic conditions do not bring about the change is shown by its absence in uremia. That such organs recover there can be no doubt, as the fact of the splenic enlargement of typhoid abundantly bears out; but the exact method of repair, of restoration, and of regeneration is not known.

The condition has been called *acute diffuse splenitis*. The term engorgement is not the proper one, and the term *infectious splenitis* has been offered as a substitute; the objections to the latter will be apparent when considering splenic infarctions.

Chronic Inflammation of the Spleen.—The fibrous thickening observed in the spleen as a result of capsular inflammation, chronic engorgement, malaria, syphilis, etc., is sometimes described as **a chronic diffuse splenitis.** In the earlier stages the organ is somewhat enlarged and is usually pigmented; the splenic pulp shows whatever alterations the associated cause may have induced. Later, there is marked increase in the amount of fibrous tissue, which fact renders the organ dense and gives to it the name *fibroid spleen*.

Perisplenitis.—In general peritoneal inflammation the serous

covering of the spleen is, of course, involved; by extension of inflammation from some adjacent tissue or viscus—such as the stomach in chronic ulcerative processes, the diaphragm in pleurisy of the left side, perinephritic inflammations, and chronic colitis involving the splenic flexure of the colon—the capsule of the spleen may become inflamed and thickened, and may form adhesions. Rarely is this observed as an acute process, but, rather, the results are seen postmortem. The whole of the capsule may be involved (*capsular fibrosis*), or only a small area; the past inflammation is marked by a layer of inflammatory tissue from 2 mm. to 10 mm. in thickness, rarely thicker, and usually adherent to some adjacent structure, diaphragm, colon, stomach, or posterior abdominal wall. On external examination the white area, if small, may resemble the scar of a past infarct; but on section its purely capsular relation will be apparent. In some instances the newly formed fibrous tissue is piled up in layers, constituting the so-called *lamellar* or *corneal fibroma* of the spleen. In rare instances the new tissue is cartilaginous. Sometimes the capsular inflammation and its associated thickening extends along the fibrous septa downward into the spleen. When the capsulitis has been uniformly disseminated over the whole organ, the mass, before section, may not resemble the spleen: during an operation it has been mistaken for a tumor; its position, relations, and attachments during life should prevent such an error, and an incision postmortem quickly exposes the characteristic splenic parenchyma. It is possible that the uniformly thickened capsule might, by contraction, lead to atrophy of the splenic structure, but it is not known that such a process ever occurs to a sufficient extent to involve the function of the organ.

Congestion of the Spleen.—In cirrhosis of the liver with obstructed portal circulation, in prolapsed or wandering spleens, in cardiac or pulmonary disease associated with venous engorgement, and during or after thrombosis of the splenic vein, more or less *passive congestion* of the spleen occurs. The organ becomes large, soft, sometimes semifluctuating, and nearly always dark in color; later, it may be rather fibroid. The conditions are analogous to the changes in the cyanotic kidney. There is usually a decided increase in the fibrous tissue, distended blood-vessels, edematous and rather fluid pulp, and considerable pigmentation.

Hemorrhage into the splenic pulp occurs in nearly all infections that prove fatal, and is, therefore, usually demonstrable in any spleen showing engorgement of the kind described on page 453. As a result of injury during delivery, and sometimes

in the infections that follow splenic hemorrhage is seen. It also occurs in the new-born as a manifestation of congenital syphilis. The hemorrhage may be diffuse or focal. The focal hemorrhages are commonly multiple, and vary in size from 1 mm. or 2 mm. to accumulations as large as an orange. Little is known of the changes that take place in areas of hemorrhage occurring in patients who recover. It is probable that the blood is absorbed, and that more or less fibrous tissue results. We certainly find marked increase in the pigmentation, but this is usually not sufficiently circumscribed to enable us positively to identify the area.

Splenic Infarction.—In no organ more clearly than in the spleen are to be seen the results of lodged emboli. The vessels to the spleen are characteristically terminal, and their distribution and ending in the splenic pulp are such that no embolus is likely to traverse the organ without being arrested. *Simple emboli* induce infarcts, distinctly conoid; on section, wedge-shaped; with, in the early stages of the process, an elevated surface; in color purplish (*hemorrhagic infarcts*), black, or of a combined tint; soft at first, later firm, and, again, after coagulation has terminated in liquefaction necrosis, soft, semifluid, or even cystic in consistency. Later, if not too large, organization and cicatricial tissue formation convert the mass into a pale and eventually white cone of scar tissue extending more or less deeply into the parenchyma of the organ; sometimes such a scar may extend down to the hilum, almost dividing the organ into two parts. In other cases the infarct contains but little blood; it does not become purplish or black, as in the foregoing, but is of a light pink, pinkish-white, or whitish hue, and hence is called *anemic* or *white infarct*. There is the same coagulation necrosis, followed by liquefaction necrosis, and probably the result is the same as in the area of the hemorrhagic infarct. The number of infarcts may be so great as to preclude counting; as a rule, there are more than one. While usually on the surface, they are not always superficial, and, while most frequently the area involved is cone-shaped, the blending of a number of infarcts may offer so misleading a picture as to require careful study for positive identification.

Infected emboli quickly produce an entirely different picture. Possibly, in the early development of the infarct, the appearance is the same; soon, however, the area involved is converted into an abscess, and as such abscesses are usually multiple, the spleen becomes studded with small pus cavities, or may show, by confluence, one or more of much larger size. It is well to remember that the soft, juicy, splenic pulp, with its open-mouthed

blood-vessels, may contain a pus so loaded with broken-down tissue and extravasated blood as to mislead the unwary.

Splenic abscess may also arise from direct injury of the spleen and from extension of suppurative processes from adjacent organs, such as perforating ulcer of the stomach, and at times without any discernible cause. The occurrence of splenic abscess in typhoid fever and other acute processes must be looked upon as resulting from pyogenic infection of an area of necrosis, itself caused by the activity of toxins circulating in the blood. It is admitted, of course, that the typhoid bacillus might possibly induce suppuration without the presence of pyogenic cocci. Actinomycotic and gummatous lesions occasionally suppurate. Splenic abscess may be single or multiple. Embolic abscesses are usually, although by no means always, multiple. Abscesses resulting from trauma and from direct invasion of the splenic tissues are commonly solitary. An abscess may be superficial or deep; its shape is largely dependent upon the cause; embolic abscesses are usually more or less irregularly conic, and traumatic abscesses are commonly ovoid or spheric. An abscess may rupture into the peritoneal cavity, into some adjacent hollow viscus, or, where the process is limited, inspissation and encapsulation may take place.

Thrombosis of the splenic vein, while rare, may occur, giving rise to edema and distention of the organ resembling the congested spleen; there is commonly more edema, and, as the process is acute, less fibrous tissue is present. The thrombus may be an extension backward from the portal vein, or, arising in the splenic vein, may extend into the portal.

Gangrene of the Spleen.—The wandering spleen may, by the twisting of its pedicle, cut off the blood supply and blood exit; the poisons produced by the disorganization of the splenic tissue favor the migration of bacteria from the adjacent alimentary canal, and, by this infection, the dissolution of the organ terminates in gangrene. The author has known two cases, undiagnosticated during life, and both found with evident infection postmortem.

Leukemia and Pseudoleukemia.—In these diseases the spleen is often much enlarged, pale or bright red, with tense capsule, and not uncommonly with adhesions to the adjacent organs. The largest spleens are found in splenomedullary leukemia, in which disease the weight of the organ may approach 8 or 9 kilograms. Accessory spleens are likely to show enlargement. The density of the organ seems to be dependent more upon the duration of the process than upon the kind of leukemia. In-

farcts are frequently present, and are often of different ages. In some cases the Malpighian bodies stand out as lightly colored nodules on the incised surface, so clearly enlarged as to be most prominent features; in other cases the cut surface is uniform. Under the microscope the hyperplasia seems to involve the entire splenic parenchyma as a lymphoid cellular growth, either shown, as previously indicated, by overgrowth of the Malpighian bodies and pulp, the former in excess, or of both structures without apparent differentiation. In leukemia the splenic enlargement may be largely due to the intercalation of leukocytes, the added white cells being of the same kind as those found in excess in the blood. In other cases the spleen contains tumor-like masses, sometimes called lymphoid growths. Such tumors vary in size from purely microscopic bodies to nodes two or three centimeters in diameter; they sometimes project on the surface of the spleen. (For blood condition in leukemia and pseudoleukemia see pp. 443 and 446, and table on pp. 448 and 449.)

Rupture of the Spleen.—As a result of violence—either directly applied, as by a blow or fall, or indirectly applied, as by the sudden arrest of the body, as in falling from a height—the spleen may rupture; when enlarged, the most trifling accident may be followed by laceration, and, when intensely engorged or softened, as in infectious diseases, the rupture apparently occurs without trauma—so-called *spontaneous rupture*. The hemorrhage is likely to be severe, but is not invariably fatal, and in rare instances, with small stellate tears, a clot may form and the organ may undergo repair by the subsequent formation of cicatricial tissue. Rupture may occur in areas of septic infarction, splenic abscesses, and cysts.

Chronic Infections of the Spleen.—The most frequent of these is tuberculosis. It is at least questionable whether *primary tuberculosis* of the organ occurs. In acute miliary tuberculosis, with wide-spread visceral invasion, the spleen rarely escapes. At times the spleen may contain a few, or more rarely many, tuberculous areas, 5 mm. to 2 cm., or in rare instances larger, caseous areas of apparently quiescent tubercle. The acute form may consist of an almost uniform invasion of all the splenic tissues with typical miliary tubercles located near the arteries, in the pulp, in the Malpighian bodies, or even in the capsule of the organ. In the larger, caseous areas of chronic tuberculosis calcareous infiltration is not infrequently present.

Syphilis of the spleen occurs in two forms—*congenital* and *acquired*. The congenital type may be manifested in one of two ways: (1) Diffuse splenic fibrosis with some enlargement, which,

however, is not usually marked, although Ziegler records an instance in which the enlarged spleen weighed 100 gm. at birth; (2) in other cases true gummata are found. The splenic lesions of acquired syphilis vary with the stage of the disease during which the organ is involved. In the earlier stages of syphilis the spleen may participate in the hyperplasia found in a number of the blood-making organs; in the late secondary or early tertiary period a diffuse fibrosis is not infrequently present; later, the characteristic lesion of tertiary syphilis—the gumma—is occasionally seen. Commonly, the lesion is solitary, but in very rare cases two or more gummata may be found. The size varies greatly; the mass is spheric or oval, of a pearly-white or grayish-white color, and is sometimes translucent, particularly at the margin. Like chronic tuberculosis, the masses are sharply defined at their margins, but, unlike the tubercular nodule, caseation is not a characteristic.

Leprosy of the spleen manifests itself as leprous nodules loaded with the bacilli in quite characteristic clusters.

Actinomycosis of the spleen occasionally occurs; with the development of the actinomycotic node, suppuration is most likely to ensue, engendering an actinomycotic abscess of the spleen.

Tumors of the Spleen.—Splenic tumors are not common. The primary tumors in an otherwise normal spleen are, of course, connective-tissue neoplasms; of the adult or typical series, hemangioma, fibroma, and lymphangioma are the forms usually met. Sarcoma is less rare. Secondary tumors are more frequent than the primary growths, and as sarcoma travels by the blood-stream more frequently than carcinoma, it is the usual secondary neoplasm of the spleen. Cancer, however, does occur.

Cysts of the Spleen.—Cysts are found in the spleen oftener than primary neoplasms. They may result from the encapsulation of massive infarcts, which, by reason of their size, have failed to organize and have not been absorbed. The usual cyst is, however, of parasitic origin, and may attain considerable size; rarely, the parasitic cysts of the spleen are multiple.

CHAPTER III.

LYMPH-GLANDS.*

The **lymph-glands**, or, more appropriately, the **lymph-nodes**, are structurally composed of a peculiar form of cells that, massed together, constitute lymphoid tissue; these, in the gland, are retained in place by a reticulum of connective tissue. The gland lies loosely in the connective tissues, and, in addition to its blood supply, receives through its capsule the afferent lymph-vessels, draining lymph from the area beyond; after passing through the gland the lymph finds its exit by way of the efferent vessel, eventually reaching the blood through the vein into which the lymph-vessel empties. The capsule of the gland is made up of fibrous tissue, with some unstriped muscle-fibers; from the capsule run septa that converge at the hilum, dividing the gland into follicles. Each follicle is made up of a reticulum, scaffolding, or sponge-like network of connective tissue, in the spaces of which are lodged the lymphoid cells; toward the periphery of the ovoid follicle the lymphoid cells are smaller than in the center, in which many of the larger form show active karyokinesis. The lymph, in passing through the gland, comes in intimate contact with the cells of the parenchyma, and in this way is probably altered in composition and cellular contents; at the same time the gland structure is exposed to whatever deleterious influences the lymph, in its return to the circulation, may bring. It will thus appear that the glands are liable to be influenced by the blood brought to them and by the lymph of the area drained.

Lymphoid Atrophy.—In the old this process is normal. It may be a *metaplasia*, the gland being more or less replaced by adipose tissue. Such glands are usually firmer and paler than normal, and may be pigmented.

Pigmentary Infiltration.—Whatever pigment the lymph may find in the tissue of the area drained is brought to the gland, and may be deposited (p. 233). Thus, in the removal of blood ex-

* The examination of the lymph-glands during a postmortem is regional: that is, the glands of an area are examined with other organs of the region, so that the consideration of their special pathology at this point, near the spleen, is due to the intimate association of their lesions with those of the spleen rather than to any special propriety of considering them at this time.

travasated into the connective tissue, the blood coloring-matter carried to the gland may be found in the cells of the gland. In anthracosis—indeed, in all forms of pneumoconiosis—the pigment from the lung is carried to the adjacent lymph-glands, where it may be deposited to such an extent as to make the gland brown, gray, slate-colored, or even black. Some of the infiltrated material, as certain calcium salts, may be removed; other solid or insoluble bodies may remain as a permanent part of the gland. The infiltrated material may induce a chronic fibroid change in the gland, with the production of fibrous tissue, thus rendering the gland more firm, larger, and less efficient in physiologic activity than normal. Whether or not normal lymph-glands are likely to be invaded by calcareous matter can not be definitely settled, but certainly an inflamed or infected gland is exceedingly prone to the deposit of lime in its interior.

Lardaceous disease affects lymph-glands as it does other tissues of the body. At times it would seem that there may be lardaceous deposits in the glands of an area without manifest general deposition in other tissues. This is said to arise as a result of the lymph bringing to the gland a material, or irritant, which leads to the change, and which, being arrested in the gland involved, permits the other tissues to escape. (See Amyloid Disease, p. 228.)

Of the *degenerative changes* in lymph-glands but little can be said. They are usually due to irritants brought to the gland, and occupy positions of secondary importance. It would seem, however, that hyaline degeneration, and possibly colloid change, may occur in lymph-nodes without any apparent or discoverable antecedent disease.

Infections of Lymph-glands.—The lymph-glands, probably more than any other tissue, possess a remarkable susceptibility to the influence of bacteria or their chemic products. There is hardly a known infection, from bubonic plague, which seems to explode its virulence on the lymph-nodes, to the most chronic infection, such as leprosy, which does not either directly or indirectly modify the structure and function of the lymphoid tissues. The change in most cases is an inflammation, a *lymphadenitis*, which may extend to the tissues around and give rise to a *peri-lymphadenitis*. As to time, the process may be fulminatingly acute, or may extend over months or even years.

In the **lymphadenitis** arising from the ordinary infections, such as those produced by the pyogenic bacteria, the appearance of the gland is greatly modified according to the stage of the disease. At first it is swollen, tense, and tender, and the obstruc-

tion to the passage of fluid through the gland may be evinced by a surrounding or overlying edema, or a swelling in the tissues of the area drained. On section, the surface is gray, grayish-white, or pink, or, rarely, there may be enough contained blood to give the incised surface a darker hue. In a gland not previously indurated the parenchyma is soft, and may be diffluent. Under the microscope the lymph-channels are distended by leukocytes, and commonly contain fibrin; in the follicles areas of coagulation necrosis, with fragmented cells, are usually abundantly shown. Later, the processes of degeneration extend beyond the follicles, involving the septa, and eventually the capsule and circumglandular tissues. Such an inflammatory process is spoken of as a **bubo.** It is common in the groin during infectious lesions of the genitalia and superficial infections of the lower extremity; it is seen in the axilla from similar lesions of the upper extremity or mamma, and in the neck when the initial process is in the superficial tissues of the scalp, face, mouth, or pharynx. One must not forget possible unusual lymphatic distribution: for example, cases in which involvement of the supraclavicular glands follows disease of the breast, the corresponding axillary glands escaping.

Suppuration of the lymph-glands fails to occur in many infections, particularly those in which the infecting organism does not possess the faculty of pus production. In these cases there is a degenerative change, a necrosis of the lymphoid tissue, with corresponding interference with function. Thus, in diphtheria the toxins absorbed from the diphtheric area give rise to edema of the lymph-gland, coagulation necrosis, and periadenoid edema, and probably lessen the phagocytic, bactericidal, or other protective powers of the lymphoid tissues to such an extent as to permit of suppuration should pyogenic bacteria be carried into the gland. The somewhat dense capsule of lymph-nodes permits the occurrence of a rather prolonged intraglandular inflammation without infection of the surrounding tissue; such a battle between the invading organism and the gland-cells may terminate in a victory for the latter, or in a drawn battle, in which case periadenoid induration and subsequent dense fibrosis, with possible calcareous change, may so surround the area of danger as permanently to include it as a "healed-in" focus. It is a limitation of this type that occurs in tuberculosis.

The gradual delivery to a gland of irritant bodies, such as may be taken up from some permanent area of infection or from dust, as occurs in pneumoconiosis when solid particles are being constantly thrown into the gland, induces a more or less subacute or

chronic productive change, during which new fibrous tissue may be formed in and around the gland, constituting *adenitis chronica* or *periadenitis chronica*, or the two lesions combined.

Of the chronic infections occurring in lymph-glands, tuberculosis and syphilis are the most important, although leprosy may involve the lymphatics.

Tuberculous lymphadenitis, the *scrofulous lymphadenitis* or *scrofula* of the older writers, arises from invasion of the lymph-glands by the bacillus of tuberculosis brought to the gland by the lymph-vessels or blood-vessels. That it is usually lymphogenous can not be doubted; but this would not account for those occasional cases, really rare, apparently no system of glands in the body escaping, and in which they all develop tuberculosis at so nearly the same time as to preclude the belief that the initial lesion was in any one area. It may be possible that these cases are general infections directly by the blood: that is, tubercle bacilli carried throughout the organism reached the lymph-spaces, and from these were transferred to the lymph-glands. Whatever may be the cause, undoubted cases of almost universal lymphatic tuberculosis occur. The frequent form of tuberculous lymphadenitis is that of some chain of lymph-glands with a fairly clear source or route of infection. Under this head come *cervical, mediastinal, mesenteric and retroperitoneal, axillary*, and *inguinal lymphadenoid tuberculosis.* The route of invasion, or, rather, the portal of entry, can often be surmised, and, although rarely, at times demonstrated. A mucosa weakened by inflammation is the most frequent route; thus, we see tuberculosis of the cervical lymph-glands following catarrhal processes of the nose or throat or inflammatory lesions in the mouth. The frequency of mesenteric tuberculosis in bottle-fed children, in whom indigestion and catarrhal lesions pave the way for the entrance of the bacillus of tuberculosis (admittedly not an infrequent milk contaminant), is largely explained by admitting the increased permeability of an already diseased mucosa. The frequency of tuberculosis of the mediastinal glands after influenza rests upon a similar basis. As already stated, the point of entry of the bacillus can sometimes be more or less accurately determined. Senn reports a case in which a nontuberculous girl wore the earrings of a tuberculous sister, and later developed a local tuberculous outbreak. The author saw a case of axillary tuberculosis follow a wound made by a corset steel on the outer margin of the breast in a young girl nursing a sister in an advanced stage of tuberculosis of the lungs; the glands were removed, and no further evidence of tuberculosis has been observed.

Morbid Anatomy.—The gland is very much enlarged, swollen, and, at first, not attached to the surrounding tissues; the gland capsule is thin and tense. On incision, early in the case, the gland is more or less hyaline, translucent, and very markedly swollen; scattered throughout its structures will be shown tubercles in different stages of development and in all degrees of necrosis and degeneration; later, these tubercles may become fibroid, caseous, or calcareous. In the mean time the gland shrinks in size and grows fibroid, with a dense and thickened capsule. Such glands as the last-described represent a "healed-in" tuberculosis, or *quiescent tubercular lymphadenitis.* In less favorable instances the process of caseation involves the whole gland; eventually, a periadenitis is induced, and the gland becomes adherent to the surrounding structures; masses of such glands may coalesce. These either break down singly or a number caseate at once, giving rise to a tubercular abscess, the contents of which are free from pyogenic bacteria. In a small percentage of the cases pyogenic bacteria may have gained ingress either with the tubercle bacilli or as a secondary infection; under such circumstances the inflammation will give rise to more marked systemic phenomena and the suppurative processes will be more active. On the whole, it may be said that tuberculosis of the glands has a tendency toward the conservative processes of sclerosis and limitation, and that general dissemination is not likely to occur; exceptions to this statement are not infrequent.

With the deposit of the tubercle bacilli in the lymph-node the evidence of infection begins. There is quickly developed an epithelioid cellular accumulation arising by a proliferation of the endothelial cells of the lymph paths; to these are added a few polynuclear leukocytes, which, with the accumulation of lymphoid cells, produce the anatomically mature tubercle. A number of these become confluent, and caseation occurs, followed by local diffusion involving the whole gland and later a periadenitis that binds the glands of the area together. The infection may spread to the circumadenoid tissues, and eventually, by the route of least resistance, may reach the skin. During this time it is possible that some of the bacilli may have passed the gland and assured further extension of the process by a second incursion through the lymph stream. (See Tuberculosis, p. 366.)

The course just described may be arrested at any point. The bactericidal action of the lymphoid structures, including the leukocytes, may terminate the process by a victory for the protective forces, the bacilli succumbing or becoming so surrounded by a protective cordon of leukocytes as to limit the lesion to the area

involved, or, possibly, to a single gland, or even to a part of a gland. This "healing-in" of a gland, part of a gland, or a mass of glands does not represent a cure, but merely a quiescent infection, which may, when the protective power is weakened by some secondary or intercurring malady, break out anew.

Syphilitic Lymphadenitis.—The nearest anatomic lymph-node draining an area in which there is an initial lesion of syphilis shows, as a rule, a reaction to the invasion, which is quickly followed by surrounding glands, and eventually, in the vast majority of cases, by the lymphadenoid tissues at large. This initial or primary glandular involvement seems to be almost purely a proliferative change in the cells of the lymphoid follicle and further blocking by leukocytes. The change is usually transitory, and disappears in a few days under treatment, and, often, in a few weeks without. In addition to this primary involvement of the glands gummata may be present in an active stage of development, or gummatous changes represented by atrophied, cicatrized, or caseous areas of a practically cured tertiary glandular change.

Under the name of **lymphadenia, lymphadenoma, lymphosarcoma, progressive lymphadenoid hyperplasia, malignant lymphoma, simple adenia, Hodgkin's disease, pseudoleukemia,** and other more or less synonymous terms, there exists a peculiar form of lymphoid change in which one or more of the lymphadenoid tissues of the body are involved, including not only the lymph-glands, the spleen, and the tonsils, but even the lymphoid tissues of the various mucosæ. The tendency at present is to regard the change observed as truly sarcomatous, and but little effort is being made at the present time to separate such glandular enlargements from the admittedly malignant growth—sarcoma of lymphatic glands.

The glandular enlargement follows no law: each case differs from all others. As a rule, the first glands to enlarge are the cervical. A cluster of glands may become prominent in a comparatively short time, may remain quiescent sometimes for months, and then may suddenly take on renewed activity. Following the cervical glands in order of frequency come the axillary and inguinal glands. In extremely rare cases the disease begins in some of the internal glands, such as the mediastinal, retroperitoneal, or bronchial; and later in the affection all these groups may be implicated.

Some of the glands may show caseous areas accurately circumscribed, and probably the result of a past tuberculous infection. The disease, however, bears no relation to tuberculosis—the association of infections is mentioned only to indicate the possibility

of combined lesions. The process is not restricted to the lymphatic glands properly so called, but the lymphoid tissues throughout the body show a certain amount of involvement. The splenic changes have already been considered. (See p. 457.) The adenoid tissue of the alimentary canal becomes conspicuous, and lymphoid growths in the liver and pancreas are occasionally found. The thymus and thyroid bodies and the suprarenal cap-

FIG. 245.—HODGKIN'S DISEASE.—(*From a photograph taken a few weeks before the death of the patient from mediastinal involvement.*)

The lymphatic enlargement in both axillæ is shown, as well as the unusual collar-like glandular involvement in the neck. The glands of the left axilla show the tuberous or nodular character of the enlargement, as they have not as yet matted together. In the right axilla the individual glands are not easily outlined. The right arm is swollen from pressure on the axillary vein, and possibly from obstruction to the lymph flow through the involved glands. At postmortem examination the mediastinal, retroperitoneal, mesenteric, and inguinal lymphatics were all found to be involved. (Patient of Professor J. C. Wilson, in the wards of the Jefferson Medical College Hospital.)

sule may be involved; rarely, lymphoid growths occur in the central nervous system.

The enlarged glands are white or grayish-white, and are either firm or soft, depending upon the rapidity of their growth; in rare cases there may be evidence of necrosis in their interior. As a rule, they remain distinct until reciprocal pressure or peripheral growth has coalesced them, and not until they have attained considerable size do they show evidence of marked periadenoid ex-

tension; to this rule there are notable exceptions, and occasionally, in a group of glands, many differences in consistency, in color, and in evidences of infiltration may be present. When examined under the microscope, great difficulty will be experienced in attempting to classify these growths. In some there may be nothing but the usual structure of a lymph-node on a large scale,—a true lymphoid hyperplasia,—while in others but little resemblance to a normal gland can be observed. Between these two extremes all stages of lymphoid tissue proliferation may be demonstrable; the gland capsule may be intact, or it may be infiltrated and the same cellular texture may be demonstrable from one gland to another.

Tumors of Lymph-glands.—If we except the foregoing enlargements from the tumors of lymph-glands, the only primary tumor of the lymph-node is the *sarcoma;* the alveolar, round-cell, melanotic, and mixed-cell forms occur in the order given. Sarcoma may be secondary as well as primary, but is less commonly so. The frequent secondary tumor of lymph-glands is cancer. In all its forms *carcinoma* involves the lymph-spaces; the extent of this involvement of the primitive lymph paths, and the portability of the invading cells, together with the resistance of the individual, determine the rapidity with which the tumor cells reach the lymph-gland. Thus, the rapidly growing, almost spheric, cells of the encephaloid spread more rapidly than the squamous or flat irregular cell of the epithelioma. (See Tumors, pp. 319 and 356.)

When the lymph-node is reached, the histology of the primary tumor is usually as fully reproduced as the gland and its surrounding structure will admit.

CHAPTER IV.

THYMUS BODY.

In the last months of intra-uterine life and during the first two years of infancy the thymus body may be justly called a gland, as it contains epithelial elements arranged in lobes, with subdivision into lobules, and a minute structure resembling that of certain glands. Even before birth displacement of the epithelial structures by lymphoid tissues is marked, and this substitution persists to the second, third, or fourth year. After this time atrophy progresses, and by the tenth year the adenoid structure has been replaced by fat and fibrous tissue, and at puberty, or shortly afterward, the gland can rarely be identified, or at most but a small vestige may be found.

Malposition and Malformation.—The organ may be absent, and there may be no evidence of its ever having developed. In other instances even in infancy it may be scarcely demonstrable. Accessory lobes, and even fully formed accessory glands, are occasionally observed. Rarely, the gland may be out of place, approaching the thyroid, or, less commonly, anterior to the heart and below its normal position ; in some instances a lateral displacement may be present, and still less frequently the thymus vestige may be found in the peribronchial connective tissues. *Persistence of the gland*, either with or without enlargement, is occasionally observed. In the absence of any distinct overgrowth it may be questioned whether any symptoms or lesions result.

Atrophy of the thymus, as previously stated, is a normal process. **Hypoplasia** of the fibrous tissue, with increase in the lymphoid structure, giving rise to considerable glandular enlargement, sometimes called **thymic hypertrophy,** is occasionally seen. Normally, the thymus gland varies in weight between 5 and 10 gm. at the stage of its fullest development. The enlarged thymus may weigh from 20 to 40 gm., and may retain a weight of from 20 to 25 gm. in the adult. Very often this persistence or enlargement of the thymus gland arises without any associated phenomena. In other instances it is observed in connection with goiter and with the lymphoid and adenoid enlargements of leukemia and Hodgkin's disease. Hérard, Bontemps,

Grawitz, Marfan, Brouardel, and others believe that enlargement of the thymus may have something to do with the occasional occurrence of sudden death, particularly in children—so-called **thymic death.** Following thymic death, as well as asphyxia from other causes, *ecchymoses* and marked congestion are commonly found in the thymus. *Petechiæ*, *ecchymoses*, or even *hæmorrhagic infiltration* are occasionally observed in the gland in scurvy and in acute infections occurring during infancy.

Little is known of inflammations, degenerations, and necroses that occur in the thymus. That the body is subject to embolism is indicated by the occurrence of abscesses in pyemia, and sometimes in septicemia.

In common with other tissues it is liable to invasion by miliary tubercles, and at times shows the caseous nodules of chronic tubercular infection. Gummata have been met with.

Primary tumors of the thymus gland are rare. By reason of the presence of epithelium, *carcinoma* is probably the most frequent tumor; however, *sarcoma* of the round-cell type is seen. Lymphoid proliferation occurs in Hodgkin's disease and leukemia.

CHAPTER V.

SEROUS MEMBRANES.

The **normal serous membrane** is composed of a flattened layer of connective-tissue cells (endothelium) resting upon a subserous network of loose connective tissue in which ramify the blood-vessels, lymphatics, and nerves. The membrane produces no secretion, but is lubricated by a transudate of serum that probably passes out between the connective-tissue cells through the open mouths of the lymphatics; these openings constitute what are known as *stomata* of the serous membranes, and, by making the serous cavity continuous with the general lymphatic circulation, render the view that these cavities are only immense lymph-spaces probably correct. The statement that the fluid normally present in the serous cavities is a transudate rather than a secretion is based upon the view that lymph is not a secretion; this matter has been already discussed, and need not be reviewed. (See Edema, p. 264.) The blood-vessels to the serous membranes are derived from those supplying the organs that the serous membrane covers; it is also probable that the lymphatic system of the serous membrane is intimately associated with that of the subserous tissues. These views, if correct, explain the inflammatory processes that occur on the serous surfaces as secondary to inflammations of the underlying organ: *e.g.*, the pleurisy of fibrinous pneumonia.

The serous cavities of the body are the *peritoneum*, the *pleuræ*, the *pericardium*, the *serous covering of the brain and cord*, the *synovial structures of the joints and tendon sheaths*, and the *bursæ*. When we examine one of these in its normal condition, we find that it is moist, smooth, shining, and transparent. The color is uniform with that of the tissue which it covers, and where two layers of the serous membrane have nothing between them but the fibrous or fibro-elastic network on which they rest, it may be practically true that the membrane is colorless. The normal serum of the cavity is a clear fluid, usually of a light straw-color; it may, however, be stained by osmosed coloring-matter, as the coloring-matter of the blood, which may pass through the heart postmortem and stain the pericardial fluid. The amount of

fluid present in any given serous membrane is dependent upon the amount in the connective tissues elsewhere, as well as the surface area of the membrane in question, and must, therefore, vary in quantity. If the patient has died slowly, and a general lymph stasis has ensued from the gradual slowing of the circulation, more fluid will be found in the serous sacs than under conditions of rapid death.

The amount of fluid that can be collected will approximate, in the peritoneum, from 8 to 50 c.c.; in the pleura, from 30 to 100 c.c.; in the pericardium, from 4 to 30 c.c.

If during life, for any reason, there is slowing of the circulation leaving a serous membrane on the organ which it incloses, there will be a disposition for fluid to accumulate in the serous cavity, just as obstruction to the onward flow of blood in any part of the body leads to the infiltration of the lymph-spaces with serum. (See Edema, p. 264.) Such an accumulation constitutes what is often spoken of as **dropsy of a serous cavity.** *Ascites*, or *hydroperitoneum*, from obstructive lesions in the liver is an example of this condition. The accumulation of fluid in the pleura (*hydrothorax*) in pulmonary edema and general dropsy is a second instance; similar conditions may cause *hydropericardium.* The accumulated fluids interfere mechanically with the function of the organs in the cavity at fault, and increase the venous congestion, which may have been the original cause.

Accumulations of serum, without any evidence of inflammation, occasionally occur in serous cavities where the membrane is infiltrated by miliary tubercles. The tubercles surrounding and obstructing the small vessels—arteriole, capillary, and vein—lead to extravasation exactly as would any other obstructive lesion. The process is most frequent in the peritoneum, where not uncommonly gallons of fluid may be, at different times, drawn off, only to reaccumulate, as in the ascites due to obstruction of the portal vein radicles in the liver.

In addition to the dropsical conditions arising from chronic disease of the heart and of the kidneys, and the local obstruction to the circulation secondary to cirrhosis of the liver, chronic or persistent irritation of any kind affecting a serous membrane is likely to induce more or less serous accumulation within its cavity. Such persistent irritation is occasionally observed in the joints, giving rise to *hydrops arthrosis*, sometimes called joint dropsy.

The fluid present in dropsical conditions of serous membranes differs materially in composition from the inflammatory exudates. Its specific gravity is usually low—1010 or lower. As a rule, it is clear; occasionally, however, it may be cloudy. Cloudiness

is more frequent in hydroperitoneum than in dropsies of other serous cavities. When the accumulation is due to obstruction of the lacteals, as it may be in the peritoneum, the milky opacity is to be attributed to the presence of fat globules. These are usually easily recognized under the microscope, and may be further identified by the usual tests for fat. (See p. 243.) It has been the custom to believe that the abundant presence of leukocytes arose only in connection with inflammation, but Poljakoff* has reported a case in which the milkiness of the transudate was apparently due entirely to the presence of white blood-cells. In Poljakoff's case the low specific gravity (1009) favored the exclusion of inflammation. In true milky ascites the fluid, on standing, usually evinces partial separation into three layers: the uppermost layer is milky or cream-like, and contains fat; the sediment is composed of leukocytes and cellular detritus, while the intervening layer may be quite clear.

The order in which the serous cavities of the body are examined is: (1) Peritoneum; (2) pleura; (3) pericardium; and (4) the serous membranes covering the brain and cord. The processes in each of these, when affected by disease, vary so little—the variation depending not so much upon the membrane as upon the surrounding structures—that we may study in detail disease affecting one of the cavities and apply the knowledge thus acquired to any or all of the other serous membranes with but slight modification: *e. g.*, the brain, being inclosed in a rigid covering (the skull), will never be surrounded by the accumulations of fluid so constantly found in inflammations of the pleura. Remembering these variations in the process, as affecting different membranes, we will consider the most convenient serous membrane: namely, the pericardium.

Malposition of the Pericardium.—Whatever malpositions affect the heart, the pericardium will accompany the heart in its abnormal place. As the development of the pericardium is dependent upon the development of the heart, the sac never occurs without its enveloped viscus.

Malformation of the pericardium occurs but rarely, and usually consists of *partial* or *complete absence* of the membrane. Do not be misled by considering universally adherent pericardium as illustrative of absence of the organ. Normally, the phrenic nerves are widely separated by the pericardium, but in those cases of absence of the pericardium that have been reported the two nerves are almost side by side. This will, therefore, aid in dem-

* "Berliner klin. Woch.," 1900, No. 1, p. 9.

onstrating that the pericardium was present at one time, and that inflammation sealed its walls together. Evidences of past inflammation are usually to be found. Adhesions to the surrounding structures, thickening of the adjacent pleura, and sometimes induration of the mediastinal tissues will offer further aid in recognizing the essential character of the process.

Maculæ albidæ, *tendinous patches*, or *white* or *milk spots* on the pericardium, are occasionally found, and are usually due to the heart thumping, at each pulsation, against some hard body, such as a prominent costal cartilage, or, more rarely, the vertebræ. These spots are to be differentiated from the deeper lesions of fibroid change in the cardiac muscle by the former being thin, superficial, and not in the muscle, but on its surface. It is generally admitted that the so-called milk spots do not have their origin in any acute inflammatory condition. Each spot is essentially a localized fibrosis, commonly restricted to the pericardium and subpericardial tissue, and rarely involving the myocardium. When the fibrosis extends into the muscle, it is usually only a very superficial invasion, although, in rare cases, local extension of the newly formed fibrous tissue into the cardiac wall may be observed. In such instances it is quite impossible to say that the condition did not first involve the muscle—an interstitial myocardial fibrosis. The spots are pure white, grayish-white, or even pearly in color; rarely, of a pinkish hue. Occasionally, a spot may be slightly calcareous. They are usually situated in the visceral pericardium near the base or exterior surface of the right ventricle or near the apex of the left. They are infrequent in childhood, and are more often present with advancing years. They are more frequent in males than in females. Enlarged hearts are more commonly affected; particularly is this the case in hypertrophy.

Infiltrations.—Pigment is rarely found in the pericardium. Fatty infiltration is occasionally observed. Calcareous areas may be seen, particularly if the membrane has ever been the seat of inflammation. Sometimes in fibrous areas resulting from past pericardial inflammation extensive calcareous infiltration is found. At times this calcific deposit may be so great that one can but wonder how the heart has maintained its contractile power; the whole of the pericardium may show more or less calcareous infiltration, and at points the calcific layer may be five millimeters in thickness. Such extensive calcareous infiltration is usually to be regarded as evidence of past inflammation, and it is doubtful whether calcification occurs in a serous membrane that has not been the seat of some inflammatory lesion.

Degenerations.—Fatty, myxomatous, hyaline, and granular changes occur, but not frequently.

Inflammation of the pericardium (pericarditis) is analogous to inflammation of the peritoneum (*peritonitis*), inflammation of the pleura (*pleuritis*, or pleurisy), inflammation of the meninges (*meningitis*).

Acute Pericarditis.—Clinically, pericarditis is said to be *acute* or *chronic;* pathologically, it would probably be better to refer to it as simple and infective, the simple form being separable into the acute or chronic, the infective depending upon the character of the infection running a rapid or a prolonged course. As all the infections are not as yet fully worked out, the clinical classification must, at least for the present, be accepted.

Inflammations of the serous membranes are said to be *primary* and *secondary*. The primary inflammations are sometimes called idiopathic, based upon the impossibility of definitely ascertaining the essential etiologic factor. Nearly all the inflammatory conditions affecting the serous membranes are secondary in point of origin, and therefore are practically always associated with some other morbid process. One of the most frequent causes of inflammation of the serous surfaces is extension of the inflammatory process from adjacent structures. Of the many examples that might be given for this condition, the following should be mentioned: Meningitis secondary to disease of the ethmoid, sphenoid, and mastoid sinuses, and from diseases of the middle ear or cranial bones; pericarditis secondary to pleurisy or mediastinitis or ulcerative lesions in the esophagus; pleurisy secondary to diseases of the underlying pulmonary tissue; peritonitis resulting from perforation of the intestine as well as from suppurative, perforative, or gangrenous processes in the appendix; and extension of infection from the pelvic viscera, particularly in the female. The circuitous route usually taken by suppurative and ulcerative processes occurring in organs adjacent to the diaphragm may lead to unusual, or even extraordinary, combinations of pathologic conditions. Thus, a hepatic abscess may induce a peritonitis or pleurisy, or both, depending upon whether its extension is directed toward the diaphragm, through which it may perforate, extending even into the lung and discharging its contents through a bronchus. Gastric ulcer and carcinoma of the stomach may perforate the peritoneum, pleura, or pericardium.

Inflammations of the serous membranes may also arise as a result of specific agents circulating in the blood. Thus, we see in pyemia and septicemia inflammations involving the joints, peri-

cardium, pleura, meninges, and peritoneum. Inflammations of serous membranes are sometimes said to be *chemic* or *aseptic*, in contradistinction to inflammatory conditions arising from demonstrable infection. Thus, it has been held that the inflammation of the joints and of the pericardium in rheumatism, for example, was due to the presence in the circulating blood of irritants probably the result of faulty metabolism. The trend of opinion at present seems to be toward the belief that rheumatism is a bacterial disease, and if such origin can be satisfactorily demonstrated, its time honored use as an example of a nonbacterial cause of inflammation of serous membranes will not be justified, and the possibility of distinctly chemic or aseptic serous inflammation must appear less admissible.

Of the various causes given for pericarditis, the following may be considered as important: Rheumatism probably leads the list. In about fifty per cent. of the cases there is a distinct rheumatic history. With the rheumatic cases are to be included pericardial inflammations attributed to cold and exposure, as it is found that these factors are often influential in determining the occurrence of pericardial inflammation in rheumatic patients. In from five to ten per cent. of the cases of chronic renal inflammation pericarditis occurs. It is sometimes a part of uremia; at other times it precedes uremia, and in some cases it occurs without other uremic phenomena. Blows over the pericardium, crushing of the chest-wall, penetrating wounds, fracture of the costal cartilages, and other forms of thoracic injury may cause inflammation. Pericarditis resulting from extension of inflammation from adjacent structures has been considered. Myocarditis, particularly of the acute suppurative form, is usually associated with a certain amount of pericardial inflammation, although the latter may be absent.

Aneurysm of the heart or of the aorta—the latter presenting in the pericardial cavity—may be associated with pericarditis. Malignant growths and chronic infectious processes attacking the pericardium usually induce inflammation. In mycoses of the blood the serous membranes rarely escape, the pericardium participating in the general infectious process. Pericarditis is occasionally seen in diphtheria, measles, and smallpox, and is not an infrequent complication in erysipelas. Gout and diabetes are present in a small percentage of the cases.

Of the many bacteria influential in the production of pericardial inflammation, streptococci, staphylococci, and the pneumococcus deserve special mention. The tubercle bacillus is usually present in pericardial inflammation secondary to tuberculosis of

the lung or pleura; but as pulmonary tuberculosis is often accompanied by a mixed infection, it is possible to have an associated pericarditis not of itself due directly to the tubercle bacillus. The bacillus coli communis may be found in pericardial inflammations, alone or with the typhoid bacillus, and is not infrequent in inflammations of the pleura; it is a frequent cause of peritoneal inflammation. Inflammations of the endocardium and of the peritoneum may be due to the gonococcus; it is not improbable that with more general infection the pericardium and pleura might suffer. Of the less common organisms, the bacillus pyogenes fœtidus, the bacillus pyocyaneus, and the bacillus aerogenes capsulatus may be mentioned as causes.

Morbid Anatomy.—In the first stage the membrane is dry, red and injected, slightly opaque, and much roughened. It may be sticky, and it always presents, over the inflamed area, a dull or velvety surface, in contrast to the shining luster of the normal. Histologically, at this stage the subserous capillaries are distended with blood. The areas of capillary hyperemia are scattered over the membrane irregularly, and look as though a smear of carmin stain had been daubed over the surface at irregular intervals; the diffuse character of the discoloration has been likened to a blush; rarely, if ever, is the hyperemic capillary distention universal. The *morbid physiology* is shown in the friction sounds discernible on auscultation, and due to the roughened and dry surfaces rubbing against each other; the pain of this stage is probably due to direct or mechanical irritation of nerve filaments, and partly to the irritation of the nerves by the application of the chemic bodies engendered by the changes in cell metabolism; it seems not improbable that the fever of this stage is due to the same bodies entering the circulation by resorption.

The second stage is brought about by the blood-vessels relieving themselves of those materials that ordinarily escape in any inflammatory process. The liquor sanguinis escapes from the distended capillaries, and passing through the stomata of the serous surface, reaches the cavity. Immediately upon reaching the surface of the membrane it splits into fibrin and serum, the former coating the surface of the serous membrane, the latter finding room in the cavity. With the transudation or escape of the liquor sanguinis the leukocytes pass by diapedesis directly into the fibrinous and serous exudate. It is also probable that the flattened connective-tissue cells are to some degree detached. Should the exudate be slight, and should the serum be rapidly absorbed, but little remaining in the cavity, clinically, the inflam-

mation is spoken of as *plastic* or *fibrinous;* if, however, the exudate

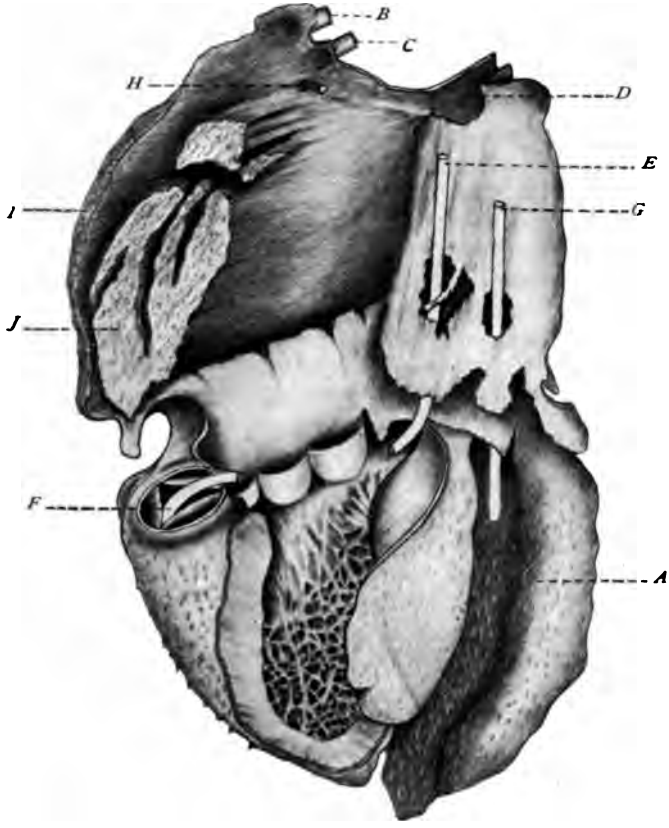

FIG. 246.—HEART SHOWING VILLOUS PERICARDITIS; ASCENDING AND TRANSVERSE PORTION OF ARCH OF AORTA, SHOWING ANEURYSM WITH CONTAINED CLOT, AND RUPTURES INTO PULMONARY ARTERY AND PERICARDIUM.

A. Part of the parietal pericardium, showing the fibrinous deposit and minute villi. A similar appearance is present on the visceral pericardium. *B*. Innominate artery. *C*. Left common carotid. *D*. Left subclavian. *E*. Catheter passing through the clot in the aneurysm of the aorta and into the pulmonary artery, following the course of the rupture into the last-named vessel. *F*. Continuation of the same catheter into the right ventricle through the orifice of the pulmonary artery. A section was cut out of the catheter in order to show position of aortic cusps. *G*. Catheter passed from the aneurysmal cavity through the thrombus and pericardium and entering the pericardial cavity into which the aneurysm ruptured. There were clinical and pathologic reasons for believing that the rupture into the pulmonary artery was old—probably several weeks. The rupture into the pericardial cavity was recent, and had been the immediate cause of death. *H*. Inferior thyroid artery. *I*. Wall of aneurysm. *J*. Laminated thrombus, through the center of which the circulation had been maintained. Above the leader from the letter *J* are shown four slit-like areas that contained dark clots of blood (red thrombi). The remainder of the thrombus was white.

be abundant and the serum be not taken up, the process is spoken of as *serofibrinous*. If the first stage be called the stage of

engorgement or hyperemia, the appearance of the exudate initiates the stage of exudation.

In this stage the membrane will be found either partly or completely covered with fibrin, the degree of cohesion being dependent upon the thickness of the layer and upon its age, as will be evident further on. The serum in the serous sac differs from the normal in that it is opaque and contains flocculi of fibrin, the opacity being due in part to the fibrin, but largely to the abundant presence of leukocytes. The soft, downy mass of fibrin hanging in shreds has led to the heart at this stage being called the *cor villosum;* it is also known as the *cor hirsutum.* (See Fig. 246.) Laennec compared the appearance to that resulting from the separation of two smooth surfaces of wood between which had been pressed a pat of butter, and hence the term "bread-and-butter appearance." The thick, shaggy layer may remain adherent to the membrane, or the fibrin may be whipped off to a greater or lesser degree by the movements of the inclosed organ. The color varies. Commonly, the inflammatory exudate is white or yellowish-white; sometimes, however, it is brown, yellowish-brown, or even brownish-red. These modifications in color are due to the dissolution of hemal elements in the exudate. In the earlier stages the exudate may be readily stripped from the serous surface, and may even show lamination, as though successive layers had been thrown out, the lowermost and overlying layers being pushed upward by the succeeding layer. The amount of serum present in the cavity determines whether inflammation should be called in this stage dry or moist. Where absorption has been rapid and the serum has thereby been removed as rapidly as formed, or nearly so, the pericarditis is said to be dry, plastic, or fibrinous. On the other hand, the amount of accumulated serum may be from 100 to 200 c.c.; rarely as much as a liter, and occasionally more.

The *morbid histology* of this stage will be found to be a reduction in the size, and a less crowded condition, of the subserous capillaries, they having been largely relieved by the outpouring of those materials that have gone to form the exudate. The layer of fibrin, on section and in teasings, will show the abundant presence of leukocytes and a few red cells, while the endothelial cells will be seen to be desquamating, the process at points being laminated, masses of these elements being discernible far up in the fibrinous layer.

The *morbid physiology* of this stage is shown in the resistance offered to the functional activity of the encumbered viscus. If an abundant exudate be present, pressure will influence the action

of the environed organ and will mechanically impede its function. Friction sounds disappear if the exudate be sufficient to force the two layers apart and the fibrin covers the roughened serous surfaces. The fever may be kept up by the absorption of the metabolic products; these also induce, not uncommonly, phenomena not usually due to pyrexia alone: *e. g.*, suppression of excretion and nervous symptoms. The fibrinous exudate may so conceal and obstruct access to the lymphatic and vascular exits as to preclude absorption of the serum or its pyrogenous constituents, and hence no systemic phenomena due to their absorption may be manifest. When percussion and auscultation can be brought into play, the phenomena associated with the presence of solid or liquid materials may be found: *e. g.*, dullness.

Exactly how long these two stages may last can not even be inferred; their duration varies, the conditions inducing the variation being but indifferently understood; the cause, the severity of the attack, the condition of the patient, whether weak or strong, are undoubted determining factors. The stages may be prolonged or brief, and just what determines this can not always be definitely stated; sooner or later, if the patient survives, repair proceeds as follows:

In this stage the connective-tissue cells, and possibly the leukocytes, present in the wall of fibrin proliferate and convert the layer into embryonic tissue; young blood-vessels are developed from the subserous layers, and lymphatic connection is reestablished. The facility with which young blood-vessels shoot up into the new tissue is marvelous, and to the rapidity with which this process of organization develops, modern surgery owes many of its great achievements. The proliferated leukocytes and young connective-tissue cells, the progeny of the endothelial lining, constitute a small, round-cell mass known as embryonic tissue; when the young blood-vessels permeate this structure,—in other words, when it becomes vascularized,—it is known as granulation tissue. The next step is the organization of this into fibrous connective tissue, which, becoming smoothed, gives a surface functionally normal; but as all organizing tissue manifests a tendency to contract, grave results may ensue in the structures beneath. Following meningeal inflammation, pressure upon nerves leaving the brain may, by constriction, lead to degeneration and entire loss of conducting power (paralyses), blindness or deafness being thereby produced. Over the lung the contraction may preclude reexpansion and favor the continued presence of the serous exudate. A band around the intestine may cause narrowing, and eventually obstruction. In the pericar-

dium, however, it is not believed that the contraction does sufficient harm to merit consideration.

Adhesions between two layers of a serous membrane—*e. g.*, the pericardium—are brought about by the two fibrinous surfaces coming together at any stage of the inflammation before organization is well under way. In the recent state the fibrinous layer of one side will adhere to its duplicate if they come in contact,

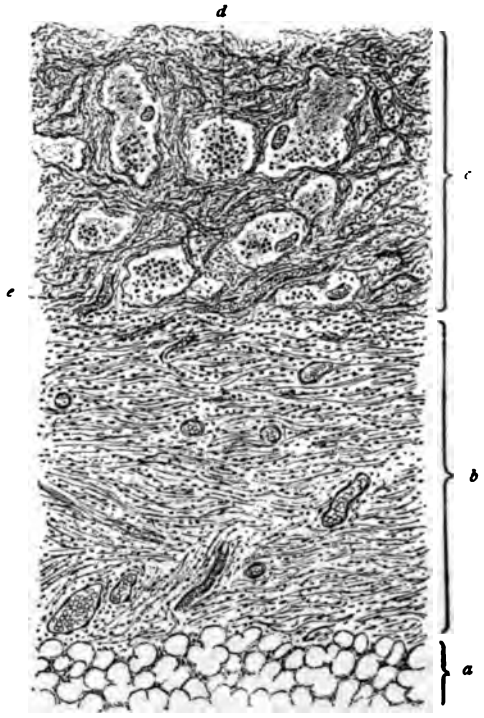

FIG. 247.—VERTICAL SECTION THROUGH AN INFLAMED SEROUS MEMBRANE AFTER THE FORMATION OF THE FIBRINOUS EXUDATE.—(*Schmaus.*) × 250 diameters.

a. Subpericardial fat. *b*. Swollen membrane, the surface of which is contiguous to and blends with the overlying fibrinous deposit *c*. *c*. Layer of fibrin in which are numerous leukocytes, *d*, and into which, at *e*, are developing blood-vessels.

and it is not improbable that in the embryonic tissue stage of the inflammation, or even when vascularization is well advanced, cohesion of the two surfaces, followed by an organized adhesion, is possible; after agglutination of the surfaces, the young blood-vessels anastomose and pass from one side to the other, organization into fibrous tissue ensues, following the lines already

indicated, and an adhesion is the result.* The constant movement of the heart probably precludes the general union of the pericardial layers at a single attack, but in the pleura it is not improbable that the entire sac may be obliterated by a single inflammatory attack. Whether adhesions form or not, the serous membrane remains permanently thickened. Into this new tissue lime salts or fat may be deposited. In the former instance the condition is known as *calcification;* in the latter, as *fatty infiltration.*

An opportunity to study the formation of adhesions is afforded in almost all surgical operations upon serous surfaces. A wound of the intestine has the two serous surfaces brought together by sutures; along the line of contact an exudation of liquor sanguinis and the migration of leukocytes occur; the former breaks up into fibrin and serum, the fibrin forming a temporary cement and binding the two apposed surfaces together; embryonic tissue is formed, followed by granulation tissue, and later by a cicatrix that binds the surfaces together along the line of suture. This cicatrix is an adhesion, the histology and mode of development of which are practically identical with the formation of adhesions in pericarditis, pleurisy, inflammations of tendon sheaths, etc. The closing or obliteration of the sac of hydrocele is brought about by inducing an inflammation of the serous membrane and favoring adhesion of the walls by withdrawal of the contents, thereby permitting collapse. The surgeon withdraws the contents and brings about an inflammation of the lining membrane by gently scratching the serous surface or by injecting an irritant, such as iodin. There is redness (hyperemia), followed by the development of a fibrinous exudate with agglutination of the collapsed walls; proliferation of the connective-tissue cells leads to repair, just as indicated in the foregoing description of adhesion formation. In this case adhesions are expected, and, as in the union of two serous surfaces when sutured, the success of the operation depends upon the development of new fibrous tissue through which union is secured.

Suppurative pericarditis results from the infection of the serous membrane by pyogenic bacteria. Whether these were present from the beginning, as after a wound of the pericardium, or whether infection followed the initial processes, matters but little. The peptonizing influence of the organisms manifests itself as soon as the development of embryonic tissue occurs; this is liquefied as rapidly as produced, and pus is thereby engendered. Vascularization is impossible while the process of lique-

* See p. 470; also compare with union by first intention, p. 298.

faction is going on, and the protracted character of the process has given the infected membrane a name descriptive of its pus-producing faculty it being known as a *pyogenic membrane*. Structurally, such a membrane is composed of cellular elements not unlike those found in the wall of an abscess (p. 291); later, the free surface continues to be rich in leukocytes, and therefore largely cellular. Within this cellular accumulation the conflict between the bacteria and the cells will continue, as manifested by the associated phagocytosis, necrosis, and pus-formation. Below this wall there is sooner or later developed a layer of fibrous tissue. As this fibrous tissue, in conjunction with its overlying cellular layer, presents a certain resistance to the further invasion of the underlying structures by the bacteria, Park has proposed the name *prophylactic membrane*. The thickening may exceed one centimeter; the membrane is usually tough, the surface being soft and downy and bleeding upon the slightest injury. The deeper layer not infrequently contains calcareous material. In the suppurative inflammation of serous membranes the fever-producing element present in the noninfective forms has its activity augmented by the addition of the pyrogenous products of bacterial life. (See p. 385.) The accumulation of pus in the pleura constitutes what is kown as *empyema* or *pyothorax;* in the pericardium, *pyopericardium;* in the peritoneum, *pyoperitoneum, peritoneal abscess, suppurative peritonitis*, etc.

Inflammation of the serous membrane is sometimes accompanied by a hemorrhagic exudate; at such time the term **hemorrhagic inflammation** is used. It occurs most commonly in connection with debilitating conditions, such as tuberculosis, asthenic states, cancer of the serous membrane, and, rarely, without any apparent cause. Trauma may lead to hemorrhage in the exudate. Tapping may rupture some of the delicate vessels of an organizing exudate, or the withdrawal of the serous exudate may remove the support to the delicate newly formed capillaries, which rupture, and thereby give rise to blood in the fluid. The hemorrhagic phenomenon may show in the serum, or it may exist as petechiæ or areas of subserous rhexis. The hemorrhagic inflammations are most frequent in childhood, although not unknown at any age. The pleura is oftenest affected. The frequency of the hemorrhagic form of pleurisy is variously given by different writers: Lewin found the effusion hemorrhagic in 4 out of 50 cases; Reimer, five times in 121 autopsies; and Israel,* twice in 206.

* "Jahrbuch für Kinderheilkunde," Bd. XLVII, 1898, No. 16.

Inflammations of the serous membranes are spoken of as *localized* or *circumscribed* when only a part of the serous surface is affected; as *general* or *diffused* when the process invades an entire membrane. Localized peritonitis is common; localized pericarditis probably never occurs. *Diaphragmatic pleuritis* is a localized inflammation of the pleura at the base. When the localized process is accompanied by the development of a walled-off accumulation of fluid, the inflammation is said to be *encysted;* rarely, such inclosed masses, when they contain pus, are referred to as abscesses: *e. g.*, of the pleura or peritoneum. They are not really abscesses, but purulent accumulations in existing cavities.

Chronic pericarditis consists in the presence of the results of the acute form, and is known as adhesive or adherent pericardium. The condition present may be that of: (1) Partial or complete adhesion; (2) large masses of fibrin whipped off in the serum may not have undergone absorption, but may remain as caseous or semisolid collections too large to be vascularized; (3) caseous areas resulting from the absorption of the fluid portion of a past pus collection or from tuberculosis of the membrane; (4) calcareous masses in the newly formed inflammatory tissues. When these forms exist, the only morbid physiology that is likely to be present will be increased work for the heart.

Tubercular inflammation of the pericardium or other serous membrane may exist in two forms—*acute* and *chronic*. The source of the infection is usually tuberculosis of some organ or tissue adjacent, as mediastinal tuberculosis and tuberculosis of the lungs, acting as causes of tubercular pericarditis and pleurisy respectively. Tuberculosis of the middle or internal ear may cause tubercular meningitis. Tuberculosis of the alimentary canal or mesenteric lymph-glands may be followed by tuberculosis of the peritoneum. Again, tuberculosis of one or, it may be, two or more serous membranes may occur as a part of an outbreak of acute disseminated miliary tuberculosis. (See p. 371.) In acute tuberculosis of a serous membrane the phenomena described when considering acute simple pericarditis will usually be found present; fibrin and serum will be found, as in the acute inflammations already described, and only after the most careful search may the tubercular origin of the process be demonstrable. Tubercle bacilli are rarely demonstrable in the serum, but may occasionally be found in the fibrin layer; at times distinct miliary tubercles may be found in the new tissue or in the membrane beneath; when, however, miliary tuberculosis exists in a serous membrane, sections, or occasionally stripping, will usually show the presence of the tubercles.

Actinomyces, glanders, and other bacterial chronic infections may occur.

Air in serous cavities is always regarded as a dangerous occurrence, and gas or air in the sac of the peritoneum has long been recognized as a certain precursor of suppurative processes. The reason is apparent: all sources of air ingress give rise to infection, the import of which need not be explained.

The presence of air or other gases in the pericardium (**pneumopericardium**) results from one of three causes: (1) Injury (50 per cent. of the cases); this includes wounds of the chest-wall or esophagus, thereby assuring the direct entrance of air.

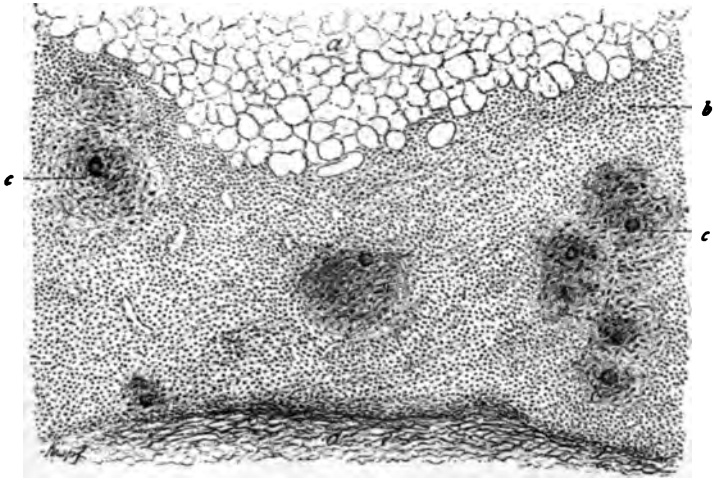

FIG. 248.—ACUTE TUBERCULAR PERICARDITIS, VERTICAL SECTION OF INFLAMMATORY EXUDATE.—(*Schmaus.*) × 250 diameters.

a. Subpericardial fat. *b*. Layer of granulation tissue that extends to the layer of fibrin. *d*. *c*, *c*. Tubercles containing giant-cells. Other tubercles are shown, in some of which degenerative changes are beginning to evince themselves.

(2) Penetration of the pericardium by ulcerative or necrotic processes originating in or invading an adjacent gas-containing viscus. With this class of cases would be included the pneumopericardiums resulting from tuberculosis or other lesions in the lung, as well as like extension from the esophagus; ulcerative processes in the stomach, and possibly in other intra-abdominal viscera, may also reach the pericardial cavity. (3) Infections of the pericardium by gas-producing bacteria. The demonstration of this source of gas in the serous cavities is now complete; the organisms found in this condition are the bacillus coli and the bacillus capsulatus aerogenes of Welch. As further proof of

micro-organismal gas-production in the serous cavities during life, if such be needed, is the occurrence in these infections of inflammable gases containing hydrogen, and therefore not derived from inspired air.*

In the large majority of cases in which air is found in the pericardium it entered postmortem; in raising the sternum, the least puncture, so small as to escape recognition, may permit air to enter the pericardium. By remembering this possibility, one is not likely to be misled.

Blood in the pericardium (**hemopericardium**) may follow rupture of the heart or the first part of the aorta, aneurysm, cancer of the pericardium, rupture of the pulmonary artery or veins, or a trauma that injures or lacerates the parietal pericardium. The quantity may be slight or excessive.

In scurvy, pernicious anemia, blood mycoses, purpura, phosphorus-poisoning, leukemia, and allied conditions, the serous membranes may be studded by pinhead-like dots of subserous hemorrhage—petechiæ.

Hydropericardium may accompany dropsy from any cause. (See Dropsy of Serous Cavities, p. 471.)

Tumors of the serous membranes may be primary or secondary. The primary tumors must, of necessity, be of the connective-tissue series, and nearly all the members of this group have been found in the serous cavities and springing from the serous membranes. For some reason not known, the omentum seems to be the most common seat of this class of the nonmalignant or adult-tissue type of the connective-tissue series: myxoma, lipoma, fibroma, chondroma, and even osteoma may occur. The embryonic connective-tissue tumors—sarcomata—are not infrequent in the serous membranes. Quite a number of sarcomata of the omentum and mesentery have come to the author's notice. Endotheliomata may arise from any serous membrane, but are most frequent in the pleura, pericardium, and meninges. The cancers or carcinomata are always secondary, as they never rise in a pure connective tissue. The carcinomata of the uterus and alimentary canal not uncommonly invade the peritoneum, multiple nodules of secondary cancer developing on the serous surface. Cancer of the esophagus, stomach, or mediastinal glands may invade the pericardium direct or by metastasis.

Of the **cysts,** dermoid may occur in the cavity of the pelvis. Purely *serous cysts* have been noticed, but their pathologic sig-

* For further reference see "Deutsch. Arch. für klin. Med.," Bd. LXI, p. 532; "Wien. klin. Woch.," Feb. 16, 1899; "Phila. Month. Med. Jour.," Oct., 1899.

nificance has not been definitely determined. *Hematomata* in the serous cavities are of not infrequent occurrence, especially in the peritoneum. The blood mass may be absorbed or it may be walled in by inflammation or a laminated circumferential clot; occasionally it may become infected. In the first instance but little evidence of its presence may in time remain. At other times absorption may be accompanied by clotting and organization of the fibrin, leaving a permanent tumor. The laminated circumferential clot may organize and inclose a cyst containing the more or less disintegrated blood.

Parasites in the Serous Cavities.—*Echinococcus* or *hydatid disease* has been observed in all the serous cavities. *Cysticerci* are at times met with in serous cavities, but give rise, in most cases, to no discernible disturbance. *Trichinæ* may be found in experimental *trichinosis* in the serous cavity, but the author has no knowledge of their occurring in the ordinary form of the disease. They probably never induce any disturbance of the serous membrane. Grosser parasites, such as round-worms, have been found in the peritoneal cavity associated with a fulminating inflammation, suppurative in character, infection having occurred as the result of the opening in the intestinal wall that permitted the escape of the worm.

CHAPTER VI.

VASCULAR SYSTEM.

HEART.*

Normal Structure.—The heart is essentially a hollow muscle divided by partitions into two distinct sides, not communicating with each other; each side is further divided by a perforated septum into two cavities, known respectively as an auricle and a ventricle. The opening through which the auricle communicates with the ventricle on each side is known as the auriculoventricular opening or orifice, and is guarded by valves that open toward the ventricle; on the right side the valve is known as the tricuspid, on the left, as the mitral. The right ventricle communicates with the pulmonary artery and the left ventricle with the aorta, the two orifices being guarded by valves opening toward the vessels. These valves are each composed of three cusps, crescentic or semilunar in outline, and known as the semilunar valves of the pulmonary artery and of the aorta respectively. The exterior of the heart is covered by the pericardium, to which reference has already been made (serous membranes); the interior is lined by a flattened layer of connective-tissue cells (endocardium) applied almost directly to the cardiac fiber, with but little, if any, loose connective tissue intervening; the valves are composed of two layers of the endocardium, reinforced by fibrous tissue, in which are a few elastic fibers. The valves of the right side, having less work than those of the left, are much the thinner, containing relatively less fibrous tissue. The endocardium, including most of the tissue that enters into the formation of the valves, is nonvascular, probably receiving its nutrition from the blood flowing over it. The cardiac muscle is of the striped variety, but differs from voluntary striped muscle; the fibers have no sarcolemma, and they inosculate by branched filaments, passing from one fiber to another; there is no bundling of the fibers, and the individual fibers are smaller than those of the purely voluntary muscle.

Size of Normal Heart.—The heart is about the size of the fist

* For method of removing the heart and completing its dissection see p. 28.

of the individual; its weight in the male varies between 285 gm. and 450 gm. (10 and 16 ounces), with a mean between 340 gm. and 375 gm. (12 and 13 ounces). The heart of the adult female weighs between 200 gm. and 400 gm. (7 and 15½ ounces); mean, between 285 gm. and 300 gm. (10 and 11 ounces). The taller the individual, the heavier the heart. The left ventricular wall is about 1.25 cm. (½ of an inch) in thickness, the right about 0.4 cm. (⅛ of an inch). The ventricular wall is thickest at its middle and thinnest at the apex.

DIAMETERS OF CARDIAC ORIFICES.—(*After Hamilton.*)

	Male.			*Female.*		
	Greatest.	Least.	Average.	Greatest.	Least.	Average.
	Inch	Inch	Inch	Inch	Inch	Inch
Aortic, ...	1.3	0.9	1.0	1.0	0.8	0.9
Mitral, ...	1.8	1.1	1.4	1.5	1.0	1.2
Pulmonary Artery, .	1.5	1.0	1.2	1.3	1.0	1.1
Tricuspid, ...	2.2	1.3	1.8	1.7	1.4	1.5

The taller the subject, the larger the orifices.

MALPOSITION OF THE HEART.

(A) CONGENITAL.

1. **Cervical Heart.**—Heart in the neck; the condition may be complete or partial, and is more frequent in the lower animals than in man.

2. **Abdominal Heart.**—Through faulty development of the diaphragm the heart may sink into the abdominal cavity; occasionally, the diaphragm does not develop immediately under the pericardium, and where the heart can not sink through the opening, an abdominal viscus may partly pass through into the pericardium, as a result of the difference between the pressure within the two cavities.

3. **Pectoral Heart.**—The heart may be developed anterior to the chest-wall; the wall may be absent, or it may have developed behind the misplaced heart; in rare instances there may be no pericardium, and less frequently the heart may be extracorporeal, —*i. e.*, outside the body,—the integument having partly closed behind it. Such conditions are not compatible with life, and are usually associated with fissural malformation of the thoracic and abdominal walls.

4. **Dexiocardia.**—A heart on the right side is compatible with life, and is recognized by insurance companies as not in any

way, of necessity, increasing the risk. Vehsemeyer states that but twenty cases of true dexiocardia have been reported up to March 18, 1897.* It is usually associated with transposition of the abdominal viscera, the liver going to the left side, etc., the combination of transposed organs being known as the *situs inversus*.

Any one of these malpositions may be partial or complete, no two cases being equally marked.

(B) ACQUIRED MALPOSITION.

The heart may be displaced by pressure applied by neighboring or adjacent organs: *e. g.*, by hydrothorax pushing the organ toward the unaffected side; under this head come the malpositions due to aneurysm and mediastinal disease.

Emphysema of both sides pushes the heart downward; emphysema of one side displaces the heart to the opposite side. Pleurisy, with contraction or a contracting fibroid pneumonia, may pull the heart toward the affected side. Hypertrophied hearts have their axes more nearly parallel with the axis of the body and nearer the median line.

MALFORMATION OF THE HEART.

1. Walls, including the septa:

(*a*) Single cavity.

(*b*) Arrest of cardiac development with a single auricle and a single ventricle, a condition permanent in the chelonia and scaly reptiles.

(*c*) Single auricle with perforate septum between the ventricles.

(*d*) Single auricle with normal ventricles or a patent foramen ovale, an attempt at closure of the septum between the auricles.

2. Blood-vessels.

As in intra-uterine life the vessels are developed from five branchial arches, it is possible to have innumerable malformations of the great vascular trunks. The following are most frequent:

(*a*) *Patent septum* between the pulmonary artery and aorta, a condition permanent in the crocodile. The fact that the aorta and pulmonary artery develop from a single trunk renders the condition possible.

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* "Deutsch. med. Woch.," March 18, 1897.

(*b*) *Transposition of the vascular trunks*, the pulmonary artery arising from the left heart and the aorta from the right.

(*c*) *Double Aorta.*—In development there are two primitive aortas, a right and a left; ordinarily the right disappears, but it may not do so.

(*d*) *Patulous Ductus Arteriosus.*—When a stenosis of the pulmonary artery develops before occlusion of the ductus arteriosus, the communication between the aorta and pulmonary artery may remain permanent. There is little difference between this and *a*, except the location, the latter being immediately at the heart.

(*e*) *Stenosis of the pulmonary artery* is probably the most frequent cardiac abnormality, excepting, of course, patulous foramen ovale. The degree of stenosis varies, and may be situated immediately at the valvular orifice or slightly beyond this point, or may be manifest in the trunk some distance from the orifice. Occasionally, stenosis is manifested in the *conus arteriosus*. Stenosis may involve the aorta.

(*f*) *Atresia* of the pulmonary artery or of the aorta is possible only with persistent communication between the two vessels beyond the point of occlusion.

3. **Valves.**—These being developed from the endocardium, may be in excess as to number of leaflets, or the reverse; a leaflet may be redundant or deficient. Care must be taken not to confuse the results of antenatal endocardial disease with malformations.

Hypoplasia of the heart occurs. The organ is small,—may be less than one-half the normal size and weight,—and usually has proportionately small vessels. The vessels may be hypoplastic without the heart showing marked abnormality. The organ may be absent.

Causes.—Malformation of the heart is dependent upon arrest or perversion of development. The stage in its evolution at which this occurs largely determines the character of the malformation. When cardiac development is arrested early, the organ shows the widest deviations from the normal. When it is delayed until later in intra-uterine life, or when the usual circulatory changes at birth fail to take their normal course, malformation is usually not marked, and commonly gives rise to no phenomena leading to a suspicion of its presence later in life.

Aside from arrest of development as a cause of cardiac malformation, there can be no doubt that antenatal endocarditis may give rise to changes in the valve leaflets or in the orifices closely allied to those seen as a result of postnatal endocardial inflammation.

Course and Termination.— Aside from those malformations which mechanically preclude the possibility of postnatal circulation, almost no cardiac deformity has been described that may not be compatible with a more or less prolonged extra-uterine existence. The accompanying lesions and associated phenomena are due to circulatory inefficiency, as manifested by tendency toward stagnation and the occurrence of faulty aeration. The mere mixing of arterial and venous blood may be unassociated with symptoms or alterations in other organs or tissues. If the blood can be kept circulating with sufficient activity to secure aeration and to prevent venous distention, the patient may escape any manifestation of the condition. The clubbing of the digits, cyanosis (morbus cœruleus), thick lips, and stubby nose with thickened alæ, may all be taken as evidences of disturbance of nutrition. The polycythemia may be truly remarkable, as in the case reported by Baunholtzer: pulmonary stenosis was present, and the blood examination showed 9,447,000 erythrocytes and 160 per cent. hemoglobin. The relatively high specific gravity of the new-born (1060 to 1070) often persists.

General atrophy of the heart occurs as the result of general wasting, with or without lessened work, the organ being very much decreased in size and weight. A specimen in the writer's laboratory weighs less than three ounces. The condition can usually be differentiated from hypoplasia by the fact that the blood-vessels remain approximately normal in size, while the corrugations of the pericardium and endocardium indicate the diminution in volume.

Local atrophy of the heart occurs in the left ventricle, and is probably a result of disuse. A stenotic mitral orifice permits but little blood to flow into the left ventricle and gives it but little work. The nutrition is also in most cases below the normal. The condition is usually accompanied by an unusual dilatation of the right side, which may also show hypertrophy. Wasting of the left ventricular wall, under the foregoing circumstances, is comparable to the hypoplasia observed in the left ventricle as a result of atresia of the aorta, or of the right ventricle when the pulmonary artery is similarly affected, in both cases the auricular septum being patulous or absent.

Brown atrophy of the heart is due to persistent congestion of the muscle, and is associated with old age, inanition, and allied conditions. The organ is of a dark chocolate or maroon color, hard and tough, diminished in size and weight, with tortuous vessels and wrinkled endocardium, due to diminution in surface. Hematoidin or hemofuchsin is deposited in the muscle-cell as a

granular pigment, near the ends of the nucleus (polar pigmentation); the fiber is shrunken, and there is also, probably, a numeric decrease. The muscle-fibers may waste to the point of disappearance. The fibrous tissue may be notably increased, and occasionally distinct areas of induration may be observed. (See Chronic Myocarditis.)

Hypertrophy will be considered after valvular disease. (See p. 512.)

Fatty infiltration of the heart occurs in general obesity; after the permanent changes incident to pericarditis; in chronic alcoholism; occasionally, in the aged and the insane. There is enormous increase in the subpericardial fat; fat-cells infiltrate between the muscle-fibers, and probably incommode their action. Some believe that atrophy of the fiber may be induced; during the early stage of the process this is not probable, as the fibers in the mass are, usually, histologically normal. The condition is sometimes spoken of as *lipomatosis of the heart.* It should not be forgotten that this condition constitutes a most frequent cause of sudden death, the overcrowded muscle-fibers failing to contract, or the fat, having penetrated between the muscle-fibers, may have weakened the interlacing network and led to rupture. The columns of fat may extend through the cardiac wall. A marked overgrowth of the fat, and persistence of the causes that lead to its accumulation, not infrequently terminate in an associated degenerative change in the muscle-fibers.

Lardaceous Disease.—*Albuminoid or amyloid infiltration of the heart* may occur in the blood-vessels of the heart and in the myocardium. The heart is undernourished and anemic; milky opacity of the endocardium of the right auricle is usually the most common macroscopic phenomenon, although any of the cavities may exhibit the change. It responds to the usual stains, but can rarely be detected except by the microscope. As a rule, the alterations in the muscle-fiber are inconspicuous, the amyloid deposit being restricted to the blood-vessels and the connective tissue between the fibers.

Calcareous infiltration of the heart may occur around the auriculoventricular orifice, usually of the left side, in the valves, in the heart muscle, and under the pericardium. If any of these structures have been inflamed, infiltration of the inflammatory products with lime salts is likely to ensue. Deposit of lime salts is not infrequent in areas of myocardial sclerosis and in old infarcts and other necrotic areas. It is also a frequent occurrence in connection with tuberculous and syphilitic lesions of the myocardium.

Pigmentary Infiltration of the Heart.—By some, brown atrophy is considered as a form of infiltration and is described under this title.

Granular degeneration of the heart, or **cloudy swelling,** is probably an initial stage in a form of fatty degeneration. (See Fig. 181, p. 242.) It occurs in infectious processes, such as septicemia, erysipelas, diphtheria, scarlet fever, and typhoid fever; in hyperpyrexia, as that of thermic fever; and in exhausting diseases generally, such as pernicious anemia. It may be associated with pericarditis or endocarditis, either as a result of the inflammation or dependent upon the same cause. The heart muscle is softer than normal, is slightly edematous to the touch, and is grayish and cloudy, in striking contrast to the bright red of the normal. Rigor mortis is absent in advanced cases. The muscle-cells are more or less loaded with granular debris, albuminoid and not fatty, at this stage, as is shown by the granules clearing up when treated with acetic acid, and not being soluble in alcohol or ether. (See p. 241.)

Fatty degeneration of the heart occurs: (1) As a general process invading the whole heart or the whole of one ventricle; (2) secondary to some local lesion, and restricted to a small area; (3) due to poisons, as phosphorus.

1. Diffuse or General Fatty Degeneration of the Heart.—This form arises from the same causes as, and is probably merely a later stage of, granular degeneration. The papillary muscles and columnæ carneæ of the left ventricle show the change to the best advantage; they are light brown in color, and running across them are yellow striæ, giving them a brindled, streaked, or flecked appearance—"tabby-cat" or "tiger" heart; at times the muscle is pale yellow rather than brown, at other times brownish-yellow—the "faded-leaf" color; in the cut wall the fiber lines just below the pericardium are lost, and the tissue appears, as a rule, uniformly yellow. Looking through the pericardium, or, better, the endocardium, the muscle shows yellow and red striæ, the latter being the unaffected fibers. The process is diffuse but not universal, comparatively normal fibers lying next to more or less altered ones. The cardiac wall may be thinned as a result of dilatation, and the orifices may be dilated. The specific gravity of the muscle is lessened. The myocardium can usually be readily pinched through. Microscopic or even macroscopic hemorrhages into the heart-wall may be present. Under the microscope the affected fibers are loaded with minute oil globules not larger than a red corpuscle. They differ from granular fibers in that the fat

is darkened by osmic acid, and may be dissolved in ether. (See Demonstration of Fat, p. 243.)

The termination of the granular and fatty metamorphoses is likely to be the same: (*a*) sudden syncope and death from failure to contract; (*b*) gradual failure by reason of increasing incompetency to maintain the circulation. Rupture of the heart is not common in diffuse or general fatty degeneration of the organ, as the cardiac muscle has not the power so to raise the intracardiac pressure as to endanger the weakened walls. It is probable that, in the granular stage, regeneration and recovery may ensue; this becomes less likely as the fatty stage advances. Clinicians commonly maintain that repair is possible even when fatty change

FIG. 249.—FATTY DEGENERATION OF THE HEART. (Specimen fixed in osmic acid, rendering the fat globules black.)
Near the center of the drawing are a number of red blood-cells. (*From a case of pernicious anemia in the Jefferson Medical College Hospital, service of Professor J. C. Wilson.*)

is advanced. Under such circumstances it is held that the destroyed fiber is absorbed and the adjacent fibers undergo hypertrophy, and in that way compensate for the tissue that has been lost. As it is not improbable that in cardiac hypertrophy new fibers are formed, with the associated enlargement of existing fibers, the possibility of a similar change following the subsidence of the disorder at present under consideration must be admitted.

2. The second form of fatty degeneration is sometimes spoken of as partial or *local*. It is due to a local ischemia, such as results from atheroma, calcification, embolic plugging, or thrombosis of some branch of the coronary arteries, which are, to a

certain extent, terminal. The lesion is manifested by the presence of a softened spot in the ventricular wall, pale yellowish-brown in color, frequently greasy to the touch, and occasionally containing oil globules, visible macroscopically. Sometimes the degenerated area is surrounded by a zone of hyperemia. The rapidity with which the process develops varies in different cases, depending upon the promptness with which the cause acts. When there has been a sudden occlusion of the blood supply, the process will commonly be rapid. On the other hand, when the local change is brought about by gradual encroachment upon the lumen of the coronary artery or a branch, the lesion will be delayed, and opportunities will be afforded for an associated overgrowth of fibrous tissue. As a rule, the degenerative change is limited to a single focus, which is located on the anterior aspect of the left ventricle near the apex. Less commonly, a corresponding point on the wall of the right ventricle is involved. The degenerated area will rarely be large, as the conditions that bring it about, if affecting a considerable extent of the cardiac wall, would cause death before the manifestation of any degenerative lesion. Occasionally, more than one area is involved. Microscopically, the changes already described are more marked than in the general variety, as the patient usually lives longer, and the small focus advances further. The process may be followed by: (*a*) Rupture, which is rare in the general degeneration; (*b*) aneurysmal bulging; (*c*) fibroid processes may convert the mass into cicatricial tissue; (*d*) the area may be so small as to give no determining phenomena.

3. The third form of fatty degeneration,—that due to poisoning,—*toxic degeneration of the heart muscle*, results most commonly from phosphorus, but occasionally from arsenic and antimony. It presents the changes already given, and responds to the general stain and chemic tests of the ordinary fatty degeneration; if an opinion is to be given in a suspected poisoning case as to the presence or absence of fatty degeneration, it must be formed, if it is possible to form such an opinion, while the tissue is fresh. The term *toxic degeneration* is not altogether appropriate, as the degenerative changes resulting from various infections are essentially of toxic origin.

Hyaline degeneration of the heart differs from the albuminoid or granular change in that the heart muscle-fibers are converted into a hyaline, vitreous substance resembling the material that results from the vitreous change in other muscles, known as Zenker's degeneration. When present, hyaline degeneration has been discovered by the microscope and not by macroscopic evidences. In hyaline degeneration the muscle-fibers may

be fragmented; the separation of the fragments may be at the junction of the muscle-cells or directly through the cell-wall. When this condition is present, Renaut has proposed the name *segmentary myocarditis.* Strekeisen believes that the fragmentation is dependent upon violent cardiac contractions during the agonal period. He holds that a preliminary weakening of the muscles is not necessary to the occurrence of fragmentation, as shown by the frequency with which it occurs when death has been due to accident and when no associated lesions can be detected.

Peculiar patches of a yellowish or grayish-yellow color, situated immediately under the pericardium, have been noticed. They usually contain bacteria, but not the tissue reactions incident to an infection. The change resembles, in a limited way, an embolic process. Weber regards the condition as a postmortem change in an area of infection, which infection occurred just before death.

Acute Myocarditis.—By some the degenerative and necrotic changes seen during acute infectious diseases, and occurring either as focal lesions involving the cardiac fibers or as a more diffuse process amounting practically to a granular or fatty change, are regarded as inflammatory, and have received the name *parenchymatous myocarditis.* In most cases myocardial inflammation is infective in point of origin, arising from the presence in the myocardium of bacteria brought by the blood or infiltrating the muscle from the adjacent pericardium or endocardium.

Acute suppurative myocarditis—*myocardial abscess* or *metastatic abscess of the heart*—usually results from infection of the cardiac wall as a result of the lodgment of infected emboli. The condition is most frequent in pyemia and septicemia, and particularly in such mycoses of the blood as commonly accompany osteomyelitis, suppurative thrombophlebitis, and endocarditis due to pyogenic organisms. In other cases the infection results from extension of bacteria from the endocardium or myocardium. The foci of suppuration are usually situated in the anterior portion of the left ventricular wall. In the earlier stages they present the gross characteristics of an infarct; later, pus may be evident, and may burrow toward the endocardium or the pericardium. The abscesses are rarely large, are not infrequently microscopic, but may attain a diameter of 0.25 to 0.5 cm. The adjacent heart muscle usually shows the changes incident to infective processes independent of actual bacterial invasion.

Chronic interstitial or sclerotic myocarditis (also called productive myocarditis, fibrous transformation, fibrous degeneration of the myocardium, and fibrous infiltration) is a chronic pro-

cess associated with the formation of fibrous tissue in the myocardium.

Causes.—Chronic endocarditis, either associated with or independent of valvular incompetency or stenosis. Chronic inflammations of the pericardium, congestion of the cardiac veins, increased venous tension, such as is seen in emphysema, interstitial pneumonia, and chronic pleurisy. It is a more or less constant lesion in failing compensation, and constitutes one of the manifestations of syphilis and of malaria. It is maintained that the

FIG. 250.—CHRONIC MYOCARDITIS.—(*Schmaus.*) × 150 diameters.

m. Cardiac muscle-fibers. *b*, *b*. Newly formed fibrous connective tissue. This can often be demonstrated to be of different ages, and in the older parts calcareous change may have occurred.

sclerotic changes of myocarditis may be consecutive to myocardial degeneration and necrobiosis brought about by various bacterial toxins. The fibrous increase has been experimentally produced by pyocyaneous toxin (Charrin), and the poison of the diphtheria bacillus is believed to lead to lesions of the muscle-fibers followed by fibroid increase (Mollard and Regaud). It is generally conceded that the fibrosis is secondary to alterations in the muscle-fiber and not the reverse. The statement that it

may be brought about by rupture of the muscle-fibers is not accompanied by any satisfactory proof.

Morbid Anatomy.—Two forms of the lesion are recognized: (1) local or circumscribed, (2) general or diffuse. *Local* or *circumscribed fibrous myocarditis* is usually attributed to a cause that has affected only a part of the cardiac wall, such as the anemia following gradual occlusion of a branch of the coronary artery, infarction, and local fatty degeneration. The fibrous area may be small, irregularly outlined, and less than one centimeter in diameter. It may or may not extend through the heart-wall. In other cases the area of fibrosis may equal one-third of the ventricular wall, and in some instances larger areas have been found. The process is most frequent at or near the apex of the left ventricle. When fully developed, the fibrous area is dense, like a cicatrix, constituting the so-called "heart-scar." Such collections of fibrous tissue probably represent efforts at repair in areas of past degeneration or necrosis. The fibrous tissue may contain pigment and calcareous matter, and muscle-fibers may be absent. When the entire thickness of the heart-wall is involved, and even sometimes when only a part has become fibroid, aneurysmal bulging may occur. The more or less sharply outlined margin at times observed has led to the belief that many of these heart-scars are really gummata. The finding of scars of evidently different ages, associated with the presence of absorbing gummata, would certainly seem to be conclusive.

Diffuse Interstitial Myocarditis.—Although diffuse, the fibrous tissue increase is commonly not uniform. The abundance of fibrous tissue between the cardiac muscle-fibers has to a certain extent justified the appellation fibroid infiltration. Most observers, as already stated, do not consider the increase of fibrous tissue an evidence of past or existing inflammation, but rather a substitutive fibrosis, the fibrous tissue having replaced atrophied, degenerated, or necrotic muscle-fibers.

Morbid Anatomy.—The cardiac muscle is usually firmer than normal; this abnormal density is not uniform in distribution. Occasionally, whitish areas of fibrous tissue may be recognized in the ventricular wall. White lines are frequently shown on the columnæ carneæ; the tendons of the papillary muscles seem to be projected as whitish streaks, often extending nearly to the base of the papillæ. Under the microscope, fibrous tissue can often be demonstrated in various states of development. Not infrequently calcareous infiltration may be present, and the muscle-fibers usually show some granular change, and occasionally pigmentation. Interference with function is always probable; it

may be slight, but in most instances dilatation comes on rapidly and gradual failure of the heart takes place.

Aneurysm of the heart results from any of the preceding conditions that lessen the resistance of the cardiac wall at any one point. Bulging occurs, the wall of the aneurysm being either a saccular mass without constriction or a large sac communicating with the ventricle by a small opening. A specimen in the writer's laboratory possesses a sac as large as an egg, its wall being made up of the endocardium, a layer of fibrous tissue, and the pericardium; the cavity of the aneurysm communicates with the ventricle by a small opening near the apex about one centimeter in diameter. In over sixty per cent. of the reported cases the aneurysm is in the left ventricular wall, usually near the apex. Rarely, the aneurysmal dilatation begins in the septum. When the aneurysm is composed of a dilated pouch communicating with the ventricular cavity through a smaller opening, thrombi are not infrequently present. As a result of roughening in the wall of the aneurysm a thrombus may form even when there is no opportunity afforded for stagnation of the blood. Sometimes the aneurysmal wall is intensely calcific. The author has observed a case in which the whole of the aneurysm was attached to the parietal pericardium, suggesting the possibility of pericardial adhesions dragging the fibroid wall outward, and in that way favoring the local dilatation, the cause of which must be principally the intraventricular pressure. Rupture occurs in nearly all cases, and death almost instantaneously follows.

Diseases of the blood-vessels supplying the heart do not commonly differ from similar alterations observed in the arteries elsewhere. The fact that the coronary arteries are more or less terminal, in the sense that abundant anastomosis is not afforded, leads to changes in the cardiac wall differing somewhat from tissue alterations secondary to vascular lesions in other organs.

Atheroma of the coronary arteries, *obliterative arteritis*, and fatty degeneration of the intima and media occur under the same conditions and from the same causes as observed elsewhere. Atheroma and obliterative change are frequently associated with syphilis, and may constitute a part of the fibroid change occurring in the organ in this disease. Both atheroma and obliterative arteritis lessen the carrying capacity of the vessel, lower the nutrition of the cardiac muscle in the area beyond, and favor the occurrence of fibroid change. Huchard analyzed 145 cases of *angina pectoris* in which the postmortem showed that in 128 of the cases the coronary artery was diseased.

Fortunately, the coronary arteries are rarely the sites of

thrombosis and *embolism*. Atheroma and obliterative change favor the occurrence of thrombosis. Embolism is less frequent. With the occlusion of the artery, the nutrition of the area beyond is suspended, and later that portion of the myocardium involved undergoes necrosis and fatty degeneration, leading to rapid softening, the resulting condition constituting a form of what the older writers called *myomalacia cordis*. (See Local Fatty Degeneration, p. 495.) With the presence of infected emboli in the blood, and possibly as a result of mural implantation of bacteria circulating in the coronary vessels, metastatic abscesses are engendered in the myocardium. (See Embolism, p. 275; also Acute Suppurative Myocarditis, p. 496.)

Aneurysm of the coronary artery is rare. It may result from atheroma or degenerative changes in the arterial wall, and is said to occur as a result of inflammation or degeneration involving the adjacent muscle. Occasionally, coronary aneurysms are multiple.

Syphilis of the heart-wall usually manifests itself as fibrous or sclerotic myocarditis; some of the cases of fibrous myocarditis are probably cured gummata. A form of fibrous myocarditis, due to congenital syphilis, has been described as occurring in the new-born. Gumma in the heart is most frequent in or near the ventricular septum, although it may occur in the ventricular wall. It is nearly always associated with a marked increase of the fibrous tissue in the adjacent muscle, and may not be sharply outlined from the surrounding structures.

Tuberculosis of the heart may occur; it is usually miliary, and is seen most commonly on the right side, immediately under the pericardium, although the bacillus has been demonstrated in the myocardium and valves. Areas of caseous tuberculosis are infrequent.

Tumors of the heart are very rare. The primary tumors are the fibroma, myoma (usually congenital and of the rhabdomyoma class), lipoma, and sarcoma. The secondary tumors are the sarcomata and cancers; the latter can never be primary. Hydatids occur in the heart.

Rupture of the heart may be caused by a number of conditions already considered, among which the following are deserving of special mention: Fatty infiltration; fatty degeneration, particularly the local form; embolism or thrombosis of the coronary arteries; and aneurysms. Ruptures resulting from blows upon the chest and crushing are more frequent on the right side or in the auricles, as the sudden rise of pressure brought about by the accident leads to yielding of the weaker walls. The ruptures depending upon changes in the myocardium

are most common in the left ventricle, as its wall sustains the relatively high systemic arterial tension. The rupture may be *single* or *multiple*, *complete* or *partial*. As many as six or seven distinct ruptures may be present. With a rupture extending through the wall or from the pericardium nearly to the endocardium, or in the reverse direction, there may be purely intramural breaks in the muscle, as shown by hemorrhages into the myocardium at the point of rupture. Ruptures are not of necessity fatal; and even when multiple, death may be delayed for days or weeks. A rupture of any size, permitting rapid evacuation of the ventricle, leads to sudden death. In the smaller ruptures that merely leak recovery is possible. The great obstacle to recovery from rupture of the heart is the fact that the conditions that bring about the rupture lessen the reparative power of the organ.

Wounds of the myocardium may not prove fatal even when the heart cavity has been penetrated. Union occurs by a fibrous tissue repair, and not by muscle regeneration. It is probable that regeneration of cardiac muscle does not occur, and that the fibroid areas occasionally found postmortem are points at which cicatrization has followed some destructive lesion involving the myocardium.

ENDOCARDIUM.

The *normal endocardium* is made up of a flattened layer of connective-tissue cells—histologically, a serous membrane. The continuous flowing of blood over its surface, and the difference in function from other serous membranes, render a separate description of its diseases necessary. The membrane is nonvascular even in its reflected layers, which, reinforced by fibrous and elastic tissues, form the valves; the valves are rich in lymphatics; immediately beneath the endocardium ramifies the plexus of nerves described by Krause. Recent investigations seem to show that the bases of the mitral and tricuspid leaflets contain some capillary ramifications; the blood-vessels do not, however, approach the free edges of the valves.

INFLAMMATION OF THE ENDOCARDIUM—ENDOCARDITIS.

Sites.—That part of the endocardium having the most work, other things being equal, will first suffer and suffer most. This explains the infrequency of the process on the right side, in adult life, and the rarity of intra-uterine disease of the left side; again, it explains those cases of secondary endocardial inflammation of the right side, in adult life, when extensive obstructive or regurgi-

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ing the ordinary staphylococci the course of the disease is rapid and the valve destruction is great and is associated with more wide-spread infection.

The organisms found include the streptococci, staphylococcus pyogenes aureus and albus, micrococcus endocarditidis rugatus (Weichselbaum), micrococcus endocarditidis capsulatus (Weichselbaum), gonococcus, and the diplococcus of pneumonia; among the bacilli occur the bacillus pyogenes fœtidus (Passet),

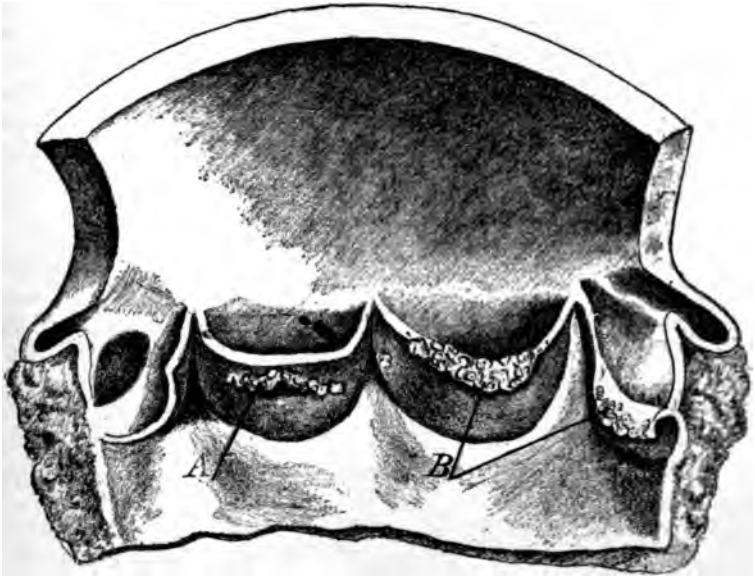


FIG. 251.—AORTIC ORIFICE LAID OPEN, SHOWING THE VALVE LEAFLETS, ACUTE ENDOCARDITIS.—(*Redrawn from Schmaus.*)

A. Line of contact with beginning formation of vegetations. *B*. More advanced and larger vegetations closely simulating in appearance an ulcerative lesion. Between the leaflet *A* and the leaflet immediately above the letter *B* is seen a single vegetation on the leaflet *B*; should a similar lesion occur at the corresponding point on the leaflet *A*, the two, coming together, could coalesce, or the continued deposit of fibrin might fuse the adjacent masses, and, by organization, would produce an adhesion between the two leaflets, thereby narrowing the orifice.

bacillus endocarditidis griseus (Weichselbaum), bacillus endocarditidis capsulatus (Weichselbaum), the bacillus of pneumonia (Friedländer), the bacillus typhosus, and the bacillus diphtheriæ. Those cases in which the bacillus of tuberculosis has been found are believed to be instances of secondary infection, the bacillus having been implanted upon a preexisting endocardial lesion.

Morbid Anatomy.—This will depend upon the stage. *First stage:* Redness and injection are not present, as the tissue is

nonvascular. (*a*) Milky opacity of the membrane, due to serum and leukocytes infiltrating the lymph-spaces and to slight roughening of the connective surface, just as grinding the surface of glass renders it more or less opaque. (*b*) Bogginess or edema of the valve is discernible at this time, and is due to the infiltration of the valve tissue by serum and leukocytes. In this softened and boggy condition, the valves pounding against one another at the rate of from 120 to 150 times a minute, (*c*) abrasion or even laceration may occur. The line of friction is the line of contact, and in this line the roughened points develop. A microscopic examination of the valve in this stage will show more or less proliferation of the endothelium, associated with desquamation, and in some cases hyaline degeneration or distinct coagulation necrosis. The subendocardial connective-tissue cells are not infrequently swollen, and the lymph-spaces of the valve may contain fibrin.

The Production of Vegetations.—The blood passing over the roughened line of abrasion has fibrin whipped out upon the rough points; to this are added proliferation of some of the connective-tissue elements and a further infiltration of leukocytes into the affected valve. These being most abundant in the focal area, increase the size of the so-called vegetation or cap of fibrin. The deposited fibrin may be granular, fibrillar, or, less frequently, hyaline. The distinctly hyaline form of fibrin is usually absent; when present, it occurs as small irregular collections in the forming vegetation. It should be observed that structurally and genetically the developed vegetation is essentially a thrombus. It may contain all the bodies commonly found in thrombi,—fibrin, leukocytes, erythrocytes, and platelets,—and is liable to secondary changes identical with those occurring in thrombi. (See Thrombosis, p. 267.)

FIG. 252.—ACUTE ENDOCARDITIS OF THE MITRAL VALVE, SECTION AT LINE OF CONTACT. (Partly diagrammatic.)—(*Rindfleisch.*) ×10 diameters.

a, *a'*. Endocardium, which at *c* has become swollen and abraded and covered by the cap of fibrin, *d*. *b*. Interstitial tissue of the valve with newly formed blood-vessels. *e*. Free margin of valve leaflet.

With firm vegetations of moderate size the lesion is called **endocarditis verrucosa**; when the collection of fibrin is large and flabby, the term **polypous** or **villous endocarditis** is at times applied.

Changes in the Fibrin Cap or Vegetation.—The vegetation may increase by layers and show distinct lamination; it may be redissolved; it may soften, from being too large to organize; if

near a corresponding mass on an opposite leaflet, especially at the valvular attachment, cohesion may occur (see Fig. 255); organization of the mass is the last process, and by some is considered as a third stage. Unless the process be fulminatingly rapid, organization has begun, at the point of attachment to the valve, by the time the vegetation is visible to the unaided eye; as organization progresses, new blood-vessels may develop from

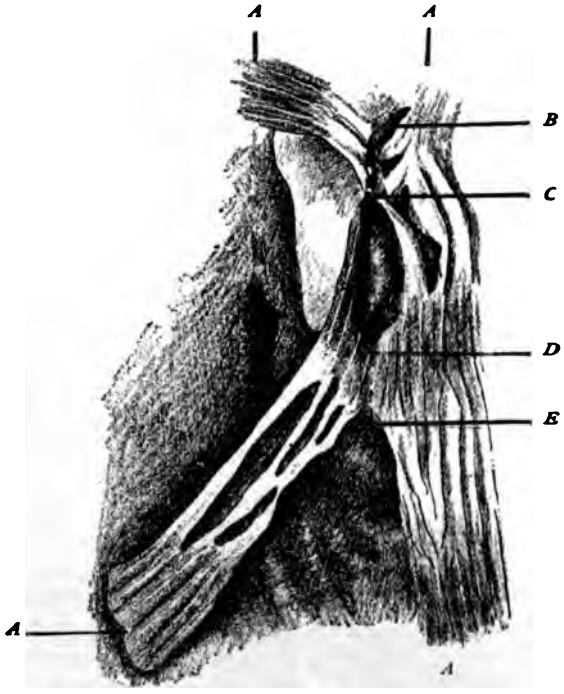


FIG. 253.—NARROWED MITRAL ORIFICE SHOWING RESULTS OF ADHESIONS WITH CONSIDERABLE FIBROID THICKENING (BUTTON-HOLE MITRAL).

A, A, A, A. Papillary muscles and tendons. *B* to *C.* Area of adhesion and fibroid thickening. *D* to *E.* Second area of adhesion and fibroid thickening. The whole free margin of the valve is intensely indurated, rendering the leaflet too stiff to close readily and, as a result of the adhesions, unable to open to its normal lumen, giving rise to both stenosis and regurgitation.—(*From specimen in author's collection.*)

the base of the valve. The presence of pyogenic and some other bacteria may limit or prevent organization and favor disintegration and softening.

Results.—(1) At an early stage the thickening or swelling muffles the valves and alters their sound; (2) fenestrations may occur if not prevented by the cap of fibrin; (3) laceration of the

valve leaflet, a further process than fenestration; (4) adhesions of valve leaflets (see Fig. 253); (5) induration, as organization occurs; (6) contraction of the valve (see Fig. 255); (7) calcareous or atheromatous changes (see Fig. 254); (8) dilatation of the valve or orifice may occur early, from the softening and edema of the initial stage, or it may follow the atheroma; (9) a single valve leaflet may relax, producing what is sometimes termed *aneurysm of the valve.*

Acute Malignant Endocarditis. —(Synonyms, *Ulcerative, Mycotic, Bacterial,* or *Pustular Endocarditis; Arterial Pyemia: L'Endocardite Vegetante Ulcereuse; Endocarditis Pyæmica; Diphtheric Endocarditis,* etc.)

Causes.—(1) Simple; may become malignant, and the chronic valve lesions are believed to predispose to this form. Goodhart found that 61 out of 69 cases had been preceded by chronic endocarditis. (2) Croupous pneumonia is the most frequent cause; in Osler's collection of cases, in 54 out of 209 recorded observations the endocardial inflammation developed during an attack of croupous pneumonia. (3) Erysipelas. (4) Septicemia and pyemia. (5) Osteomyelitis, probably due to this condition being commonly accompanied by septicemia or pyemia. (6) Puerperal fever. (7) Gonorrhea. (8) Enteritis. (9) Rarely, tuberculosis, typhoid, diphtheria, rheumatism, or chorea.

The bacteria present: Streptococcus pyogenes; micrococcus pyogenes aureus, also albus, cereus albus, and cereus flavus; the diplococcus pneumoniæ, bacillus fœtidus, and the alleged micrococcus endocarditidis. (See microbic causes of endocarditis on p. 504.)

Injury or previous disease of the valve favors the occurrence of infection, and therefore predisposes to this form of endocardial inflammation.

Site.—(1) Contact line of valves; (2) at base of valves; (3) mural. There is a form secondary to myocardial infection presumed to be due to infective embolism of the coronary artery. As to orifice, Osler, Sansom, and Hamilton accept the following order: (1) Mitral; (2) aortic; (3) aortic and mitral; (4) heart-wall; (5) tricuspid; (6) pulmonary. The valves of the right side of the heart are more frequently affected in this form of endocardial inflammation than in the acute simple endocarditis. This is to be explained by the fact that in such infectious diseases as suppuration, erysipelas, osteomyelitis, puerperal fever and other infections of the genito-urinary organs, ulcerations of the intestine, suppurative processes in the liver, and otitis media, the venous blood returns to the heart charged with the bacteria, and

hence the valves first subjected to the danger of infection are those of the right side. Following Virchow, most observers are inclined to believe that the infection is the result of direct implantation of bacteria upon the valve segments, although Köster has strongly urged the possibility of infection through the blood-vessels of the leaflet. The almost complete absence of blood-vessels in the normal leaflet, and the fact that bacteria are most abundant in the periphery of the lesion, would favor the view first given.

Morbid Anatomy.—Whether preceded by simple inflammation or not, necrosis, ulceration, and loss of tissue are almost constantly present. Ulceration in the sense that a distinct recognizable or anatomically perfect ulcer must be developed is not at all necessary. Bacteria are invariably present during the active stage of the process, and are usually most abundant in the superficial layers of the vegetation, although they are not infrequently present at the bases and in the interstices of the valves. Vegetations are usually large, although well-marked cases are found in which they are small. They usually show evidences of necrosis, softening, and fragmentation. As a result of these changes, embolism, with the development of suppurative processes in other viscera, usually accompanies this form of endocarditis. The necrotic processes are not restricted to the vegetation alone, but may involve the valve leaflet, which is sometimes totally destroyed. Mural lesions are not infrequent; they sometimes depend upon direct inoculation from bacteria in the blood; in other cases their location would indicate that the vegetation had, by contact, inoculated the ventricular, auricular, or aortic wall. Cases occur in which it is possible to believe that the infection involved the heart muscle as a result of dissemination through the blood by way of the coronary artery.

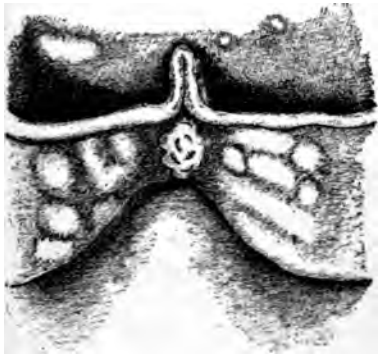


FIG. 254.—ADJACENT AORTIC CUSPS, SHOWING A SMALL VEGETATION DEVELOPING JUST BELOW THE POINT OF AN OLD ADHESION.

Calcareous areas are indicated by the white areas on the valve leaflet. A case of acute endocardial inflammation ingrafted on chronic lesion.

Microscopic abscesses are sometimes to be recognized in the valve tissue, and similar areas of a larger size are occasionally

observed in the myocardium. The extension of the infection to the myocardium may lead to penetration or perforation of the ventricular septum, aneurysm, or rupture of the heart. The calcific deposits occasionally observed in this form of endocarditis may be due to the fact that the lesion is ingrafted upon an old endocardial change in which calcification was present. In other instances there is reason to believe that the infiltration is secondary to the acute process with which it is found.

Results.—More or less destruction of tissue; infected embolic and disseminated infarction processes throughout the organism. Rarely, if ever, the patient recovers; if so, cicatrization and deformity of the affected area result.

Chronic Endocarditis. — (Synonyms, *Indurative*, *Fibrous*, *Sclerotic*, *Adhesive*, *Interstitial*, or *Permanent Endocarditis.*)

Causes.—(1) The result of the acute forms; (2) alcohol; (3) syphilis; (4) gout; (5) excessive work for any one valve, rarely all the valves, and usually only those of the left side.

The results of acute endocarditis have already been described. The true chronic endocarditis consists essentially of a progressive fibrosis involving the valves and sometimes the mural endocardium. The interstitial fibroid change develops slowly, showing as a milky opacity first at the margin of the leaflet, gradually extending, increasing the thickness and lessening the pliability of the valve, sooner or later contracting, and undergoing calcareous change. The newly formed fibrous tissue frequently shows necrotic and degenerative processes, and commonly contains areas of calcareous infiltration. Degenerative changes in the overlying endothelium may expose the calcareous plaques; the presence of projecting spicules of calcific matter leads to the deposition of the blood platelet followed by fibrin, so that, even in this form of endocarditis, small fibrinous collections are occasionally seen. As contraction ensues, curling of the valve edges, insufficiency, and stenosis may develop. In figure 250 the valve leaflet on the extreme right is beginning to show slight eversion. The chordæ tendineæ thicken, agglutinate, or shorten, so that the muscle may appear to be inserted immediately into the valve cusp; narrowing and adhesion leading to such conditions, for example, as the button-hole mitral, funnel mitral, etc. As

FIG. 255.—ADHERENT AND THICKENED VALVE LEAFLETS.—(*Rindfleisch.*)

View obtained by looking downward upon the aortic valves from the aorta. Two leaflets are adherent, all are contracted, thickened, everted, and unable to open widely or close tightly.

the sclerosis advances, the calcific changes become more marked, and eventually the valves and walls of the orifices are converted into hard, calcareous, fibroid structures, with scarcely a normal element remaining. The mural form of chronic endocarditis is secondary to atheroma or interstitial myocarditis, and shows merely as hard, fibroid, or calcareous areas on the cardiac wall.

Results of Endocarditis.—When the valve does not return to the normal, which in rare cases may occur, the changes already described lead inevitably to one of two conditions or to both.

1. Narrowing, Obstruction, or Stenosis.—This condition may be brought about in any of the following ways: (*a*) Vegetations projecting into the lumen when the valve is open; (*b*) stiffened valves that do not open; (*c*) contracted valves that can not open, but subtend the orifice like a cord; (*d*) adherent valves, the adhesions preventing opening; (*e*) eversion or inversion of a leaflet either as a part or a whole; (*f*) a lacerated leaflet hanging in the current; (*g*) contraction of the orifice incident to a circumferential inflammation at the base of the valve, or, in the mitral, the free margin; (*h*) loss of elasticity of the orifice owing to fibrous or calcareous change, or to both, without of necessity contracting, but being inelastic, it is practically a stenosis; (*i*) combinations of these processes.

2. Insufficiency or Incompetency of the Valves, Permitting Regurgitation.—(*a*) Valves may be propped open by a vegetation; (*b*) valves may be too stiff to close; (*c*) contracted valves can not close, for the same reason that they can not open; (*d*) inverted, everted, or lacerated valves can not close the orifice; (*e*) fenestra below the line of contact permit regurgitation; (*f*) contraction of the orifice leading to wrinkling of the leaflets is by some supposed to be a cause; (*g*) relaxation, distention, or dilatation of the orifice beyond a size that the valve will cover or close.

Influence of Stenosis and Insufficiency on Cardiac Work.—It matters not which of the above processes occurs, the inevitable consequence will be increased work for the heart, and this must lead to either hypertrophy or dilatation. It is not possible, in the space available, to take up in detail the physics of the normal circulation, with which it is presumed that the student is familiar, nor can the disturbances brought about by stenosis and insufficiency be fully considered. It is, of course, evident that either of these conditions affecting the orifice through which the ventricle is normally emptied more profoundly influences the function of that structure than when it is the orifice through which filling occurs. With the occurrence of aortic stenosis the work of the left ventricle must be increased, as it necessarily requires more

force to deliver 100 gm. of blood through an orifice 0.9 inch in diameter than it would if the orifice possessed a diameter of 1.3 inches. Were there not so many factors to be taken into consideration, it would be theoretically possible to calculate the amount of increase in cardiac work that would result from a one-tenth reduction of the sectional area of the aortic orifice. The cardiac work is also increased by insufficiency or regurgitation, for if 100 gm. of blood have been delivered into the aorta during the previous systole, and if 25 gm. return to the ventricle by reason of insufficiency in the aortic valves, the ventricle at the same time receiving its normal inflow from the auricle, it must be apparent that one-fourth of the blood is being pumped into the aorta twice in order to assure its progress. It of necessity follows that the heart is doing one-fourth of its work over, which, of course, implies an enormous increase in cardiac labor. The same hypotheses applied to the auricles would not yield the same conclusions; the auricular cavities communicate directly with their respective venous systems, so that the venous system of the side in question must always be considered practically as a part of the auricle. Nevertheless, it is evident that regurgitation through the mitral orifice must increase the work of the heart, as when the left ventricle contracts, a part of its force loses its effectiveness by the fact that the insufficient mitral permits a backward flow into the auricle. During the next diastole the ventricle should receive its normal quota of blood plus the blood that was regurgitated into the auricle through insufficient mitral. This, of course, means increased work for the ventricle. Mitral stenosis acts differently,—at least, when marked,—as already referred to when considering local atrophy of the heart. (See p. 491.) In the presence of increased cardiac work brought about in ways that have just been mentioned, hypertrophy or dilatation must of necessity follow.

HYPERTROPHY AND DILATATION.

Hypertrophy—	*Dilatation*—
Simple.	[Simple.]
[Eccentric.]	With thickening.
[Concentric.]	With thinning.

Simple hypertrophy is increased weight with increased functional power, without evident alteration in the cavity.

Eccentric hypertrophy is assumed to be increased weight, with increased (?) functional power and increased cavity; in other words, it is the same as *dilatation with thickening;* during life the

symptoms, if any presented themselves, were those of dilatation rather than hypertrophy.

Concentric hypertrophy is assumed to be hypertrophy at the expense of the cavity: that is, increased weight, etc., with diminution in the size of the cavity. It is a postmortem change, or is dependent upon the conditions that determine death. How easily one may be misled is illustrated by the following experiment:

Obtain three bullocks' hearts immediately on slaughtering. In one heart all the vessels should be ligated before the animal is bled or the vascular system opened; let the second heart remain empty. The third heart is to be distended by ligating the pulmonary veins and attaching the aorta to a hydrant. It is best that all the hearts have about the same weight. In a few hours, when rigor mortis has ceased to act, the following will be found: The first heart is an example of hypertrophy with a normal cavity; the second, hypertrophy with diminished cavity; the third, hypertrophy with increased cavity. As death may arrest the heart in any degree of distention, or rigor mortis act to any degree, the foregoing conditions may all be found in any hypertrophied heart. Simple hypertrophy therefore remains.

Dilatation with thickening is admitted, as is **dilatation with thinning**; but *simple dilatation* implies a larger cavity, with wall of normal thickness, and as such a heart must weigh more, it requiring more muscle to surround a large cavity with a wall of a given thickness than a smaller cavity, as the normal, the condition is one of dilatation with increased weight or thickening.

Causes of Hypertrophy and Dilatation.—Increased work with abundant nutrition are followed by hypertrophy. Overwork—that is, work beyond the nutrition and muscular power of the organ—leads to dilatation.

These may be due to conditions *intracardiac* or *extracardiac*.

Intracardiac Causes.—(1) Any of the valvular lesions already given that increase the cardiac work (p. 510); (2) myocardial sclerosis; (3) overstimulation of the cardiac muscle, as may result from the excessive use of alcohol, tea, and tobacco.

Extracardiac Causes.—(1) The various forms of chronic pericarditis—adhesive, caseous, etc. (2) Diminished caliber of the vessels transmitting the blood: *e. g.*, narrowing or hypoplasia of the aorta; contraction of the arterioles, as occurs in Bright's disease. When the blood-vessels lose their elasticity from any cause, the work of the heart is increased. (3) Increased muscular work demanding extra supply of blood, as in laborers and athletes. Hypertrophy is a physiologic process in gestation.

Hypertrophy of the left ventricle is by far the most common, but hypertrophy of the right occurs not infrequently. Those of the preceding causes that may here act are apparent, and to those may be added: (1) Stagnation of blood due to mitral disease; (2) narrowing of the pulmonary blood-vessels, as in congenital stenosis of the pulmonary artery; reduction in the vascular area of pulmonary artery, as in emphysema, interstitial pneumonia, etc.; (3) valvular lesions of the right side; (4) tumors and aneurysms pressing upon the pulmonary artery.

Morbid Anatomy of Hypertrophy.—The apex is broadened, the wall implicated is extended and forms the apex, the conic shape is lost, the muscle is red and firm, cutting with more than the normal resistance. The test is increased weight; hearts weighing over 1800 gm. have been reported. Reference has already been made to the unreliability of measuring the cardiac wall. Histologically, there is probably a numeric increase of muscle-fibers, and during the active stage an increase in the size of both the new and old fibers.

Life History of Hypertrophy.—Hypertrophy is not a disease, but a definite physiologic process with the distinct object of meeting a demand for more cardiac force: just as any muscle responds to an increased demand for power, the heart may respond. It is, however, imperatively necessary that the demand be not too suddenly developed, and that abundant nutrition be supplied to attain the desired end. It will be noticed that most of the causes already given are progressive in character and permanent in action, and will, therefore, indefinitely increase the demand for work; or advancing years, with the concomitant changes in general nutrition, or the inroad of other diseases, such as Bright's disease, will reduce the nutritional value of the blood and lessen the available food supply for the heart. In either case the compensation that nature has attempted may be overthrown by the wasting that the new changes will induce. In the earlier stages of stenosis and insufficiency abundant nutrition and slowly increasing work favor the occurrence of hypertrophy, with which there may be a certain degree of dilatation. The hypertrophy, however, exceeds the dilatation; with the increased cavity there is a proportionate increase in the volume of muscle. Later, dilatation gains on the hypertrophy, compensation fails, and the circulation, possibly for the first time, begins to manifest evidences of embarrassment. Hypertrophy then passes into dilatation.

Acute dilatation, or *dilatation not preceded by hypertrophy*, undoubtedly occurs, and merely shows that the initial nutrition can

not supply the initial demand; ordinarily, this is met by the reserve force of the organ, but this may be deficient as the result of general malnutrition or local disease, as occurs in granular degeneration and myocarditis, or the work suddenly thrown on the heart may be beyond the power of the reserve force; in either case the inability of the organ fully to perform its function leads to a gradual accumulation of blood within the cavity, and dilatation results. Acute dilatation occurs in mountain climbing, after severe exertion, and sometimes during excitement; suddenly developed valvular insufficiency, as from laceration or rupture of a leaflet, may bring about the same result.

Chronic dilatation usually follows hypertrophy, as previously mentioned, when compensation can no longer be maintained.

Morbid Anatomy of Dilatation.—Most common on the right side, and most marked in all the cavities in aortic incompetency. The auricle never hypertrophies without dilatation, and may attain an enormous size. Dilatation of a cavity leads to dilatation of the orifices that communicate with it, and hence to incompetency. Opacity of the endocardium has been noted. The muscle-fibers not uncommonly show advanced degenerative change, and in some cases a well-defined interstitial myocarditis may be present.

Degeneration of the cardiac ganglia has been observed.

Influence of Cardiac Inefficiency on Other Organs.—*Lungs.*—Edema, congestion, brown induration, pulmonary apoplexy, bronchitis, croupous pneumonia.

Liver.—Congestion, red or cyanotic atrophy, occasionally fatty.

Kidney.—Cyanotic induration; infarction.

Spleen.—Congestion may render the organ black or scarlet, and is usually attended with more or less induration; infarction is not uncommon.

The *mucous membrane of the stomach and intestine* becomes edematous, and may contain punctiform hemorrhages.

BLOOD-VESSELS.

ARTERIES.

Normal Structure of an Artery.—(*1*) *Tunica adventitia*, or areolar sheath of fibrous tissue. (*2*) *Tunica media;* (*a*) in the larger blood-vessels this is largely composed of elastic tissue with but little muscle-fiber; (*b*) in the arterioles the involuntary fibers predominate and but little of the elastic tissue is present. (*3*)

Tunica intima is histologically identical with the endocardium, and is known as the endangium; it lines the interior of all the blood-vessels and constitutes the wall of the capillary.

Arteritis.—Inflammations of the artery may be manifest in the external coat and surrounding tissues—*periarteritis;* in the internal coat—*endarteritis;* and in the middle coat—*mesarteritis.* Many of the conditions ordinarily described as inflammatory and grouped under the term arteritis are composite processes, partly degenerative and partly inflammatory. In other instances inflammatory lesions may precede degeneration or degeneration may occur in the cellular accumulation of past inflammatory processes.

I. Atheromatous Arteritis.—(Synonyms, *Endarteritis Chronica Nodosa, Endarteritis Deformans.*)

Causes.—(1) Kidney disease, particularly chronic interstitial nephritis; (2) old age, men more commonly than women; (3) syphilis; (4) gout and rheumatism.

Sites.—(1) Arch of aorta; (2) thoracic and abdominal aorta; (3) iliac arteries; (4) cerebral arteries, especially at the base; (5) rarely, arteries of the limbs; (6) occasionally, in the pulmonary artery; (7) in almost any of the large arterial trunks, particularly around the orifices of smaller branches given off; thus, in the aorta the exit points of the coronary arteries and each intercostal branch may be surrounded by a rim of atheroma.

Morbid Anatomy.—(1) Milky opacity of the tunica intima, never universal, but confined to patches here and there; (2) elevation of these patches, due to cellular infiltration and thickening; (3) fatty change in the patch, showing as a pale-yellow spot in the center of the patch, which spreads throughout the entire area; (4) deformity of the vessel, such as button-like elevations, usually most marked where a branch is given off; (5) changes in the spot—ulceration or calcification. All these processes may be evident in the same vessel.

Morbid Histology.—Excess of fibrous tissue without blood-vessels; hence the tissue tends to become fatty. The degeneration commences near the media. The new tissue disintegrates, forming a small cavity filled with granular debris, oil globules, and occasionally cholesterin. Degeneration may spread to and invade the media; the intima may give way, causing an atheromatous ulcer. The cellular infiltration of the arterial wall may be first manifest or most marked around the branches of the vasa vasorum.

Effect.—Loss of elasticity, weakening of the wall, and increased liability to aneurysm. The arterial tube being made rigid,

increases the cardiac work. When the process develops around the exit of branches,—as, for example, the coronary artery,—it may lessen the carrying capacity of the branch.

II. Arteritis Obliterans.—*Causes.*—(1) Tertiary syphilis; (2) contracting kidney; (3) it is present in areas of tuberculosis; (4) physiologic process in the vessels of the fetus, which become

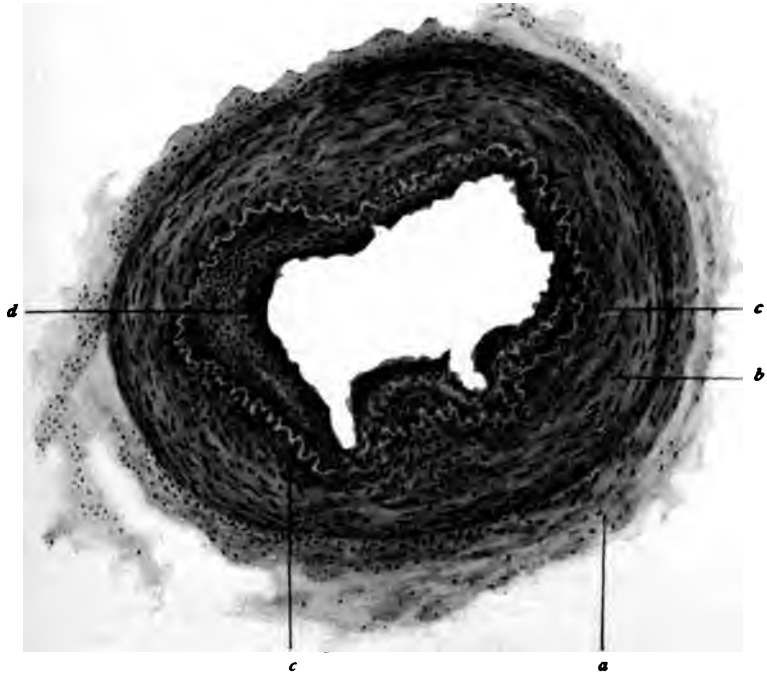


FIG. 256.—OBLITERATIVE ENDARTERITIS.—(*The tissue from which drawing was made was removed from near a cancer of the face, and prepared in the laboratory of the Jefferson Medical College Hospital by Dr. Thomas Leidy Rhoads.*) 1-inch objective, 1-inch ocular.

Specimen fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a*. Adventitia. *b*. Media. *c, c*. Elastic lamina. *d*. Irregularly thickened intima. The gross specimen was hard, cord-like, but not nodular.

useless at birth, and in the arterial supply to the parturient uterus; (5) complete or partial occlusion of the vascular lumen.

Site.—Arteries of the brain and in the blood-vessels in areas of chronic infection: *e. g.*, gummata and tuberculosis.

Morbid Anatomy.—(1) Universal cord-like hardness; (2) lumen barely discernible, or the vessel may be closed. Outline of the vessel, as a rule, uniform, but may have annular or nodular thick-

enings. There are none of the yellow patches of the atheromatous variety. Baumgarten regards the annular and nodular thickenings as perivascular gummata. Intima becomes milky, as in atheromatous endarteritis, but does not become fatty; the sclerosed areas are uniform; thickened intima encroaches on the lumen; young blood-vessels develop to supply the new tissue; hence fatty degeneration is absent. Differs from the atheromatous in that (*a*) it is a disease of small arteries, not large ones; (*b*) thickening is circumferential; (*c*) thickening becomes vascular and not fatty; (*d*) obliterates and does not favor aneurysm; (*e*) other signs of syphilis or other chronic infection are not uncommonly present.

Effects.—(1) Cuts off blood supply to tissues. In the brain softening and paralysis ensue; neuralgia, if the root of the fifth nerve be implicated. (2) In the fetus destruction of an organ, as the kidney, results from cutting off the blood supply during development. (3) Prevents hemorrhage, as in tubercular and other ulcerative processes.

III. Arteritis Infectiosa.—Includes the *suppurative*, *malignant*, or *ulcerative* inflammation of the arteries. It may be (*a*) *mural* and (*b*) *interstitial*.

Causes.—Introduction of pathogenic bacteria into a blood-vessel: *e. g.*, from wounds, periarterial infection, septic thrombi, septicemia, pyemia, etc.

The *mural* variety is due to the direct implantation of bacteria on the surface of the intima; the changes that ensue are analogous to those of malignant endocarditis. The implantation may be primary or secondary.

The *interstitial* form may follow injury with infection or may occur as the result of a general infective process. It may follow the mural form. In some instances it probably represents infection by the vasa vasorum. Inflammation terminating in pus-formation occurs in the media or adventitia, or both. There is also proliferation or, it may be, necrosis of the cells of the intima, producing roughness, which favors deposition of platelets and leukocytes, and in turn leads to fibrin formation or deposit on the vessel-wall. Thrombi so formed are prone to break down and give rise to infective emboli. The same process occurs in the veins: *e. g.*, infected uterus; infected cranial sinuses from mastoid disease.

When an inflammation involves an artery by extension from contiguous tissues, the process is spoken of as a *secondary arteritis*, and partakes of the essential features of the inflammatory process that caused it.

IV. Endarteritis Verrucosa, *or Warty Endarteritis.*—The condition is rare, and is probably the result of organized thrombi on the vessel-wall; it is usually found in the larger vessels—the aorta or the iliac or femoral arteries.

Morbid Anatomy.—Smooth warty growth on the interior of the vessel, the same color as the intima, and projecting into the lumen of the vessel.

Morbid Histology.—The mass is at first composed of young cell elements, and later, for the most part, of fibrous tissue covered by endothelium.

V. Periarteritis Simplex (*Charcot*).—This condition is non-suppurative, occurs in the vessels of the brain, and leads to miliary aneurysm. It first attacks the adventitia as a small cell infiltrate, which invades the media later, and the intima last, if at all. The softening weakens the vessel and leads to aneurysm. The disease is most common in the smaller arteries, but may invade the capillaries or the larger arteries of the base.

While the cause is not established, syphilis seems able to induce the change.

VI. Periarteritis Nodosa.—This condition has been described as occurring in the vessels of the heart (coronary artery), stomach, kidney, spleen, and muscles. As a rule, the smaller vessels alone are involved. Macroscopically, the irregular nodular enlargements vary in size from 1 or 2 mm. in the smaller vessels to 0.5 cm. in the larger. It has been thought that the affection did not involve the blood-vessels of the brain, but recent studies by Schrötter* would indicate that the cerebral vessels may be affected. The vessels are at points dilated, and at other points contracted. An abundant cellular infiltration occurs in the outer coat of the vessel; the media becomes fatty, but the intima is not affected. The small sac-like dilatations not uncommonly contain clots.

Arteriosclerosis.—Under the name arteriosclerosis have been considered a number of conditions, either associated or occurring independently. Many writers on the subject have grouped the lesions already described, and, by reason of the fact that they are occasionally associated, assumed that they were but different expressions of a general process. Gull and Sutton apparently intended to restrict the process to changes in the capillary and arteriole walls associated with an increase in fibrous tissue; to this condition they gave the name *arteriocapillary fibrosis.* As the clinical studies of the condition were extended, it was

* "Wiener klin. Wochen.," April 15, 1899.

observed that atheroma, periarteritis simplex, etc., were not infrequently associated with the change in the arterioles and capillaries. This led to grouping all these conditions under the one term—arteriosclerosis. Thoma concluded from his studies of the process that it was not to be restricted to the arteries, but that it involved the whole circulatory apparatus, and hence he termed the condition *angiosclerosis*. Having considered the changes observed in atheroma, arteritis obliterans, and the forms of periarteritis, an idea may be formed as to what is meant by arteriosclerosis in the clinical sense, if it is assumed that all of the foregoing are but different manifestations of the same process.

Old age is said to be one of the causes; the presence in the blood of the poisons of gout and rheumatism, and of the irritant bodies, whatever they may be, which induce chronic interstitial inflammation of the kidney, are important factors. The excessive use of nitrogenous food, the abuse of alcohol, poisoning by lead (chronic form), and the poison of syphilis are active causes.

That atheroma, obliterative changes, and arterial degenerations are largely due to increase in the blood pressure is indicated by the fact that under normal conditions the pulmonary artery is rarely involved, but in mitral stenosis, with increased intravascular tension in the lung and marked rise in the blood pressure of the pulmonary artery, the vessel not infrequently shows atheroma; and in cases in which the right ventricle hypertrophies, and thereby further raises the pressure, atheroma may be widely distributed in the pulmonary artery and its branches. Exactly what raises the blood pressure of the left side is not always easily determined. The method by which it is raised is, of course, more readily comprehended. Thus, if it is assumed that the heart increased its output of blood into the aorta, and at the same time there was no yielding in the arterioles throughout the body, the arterial tension must rise. On the other hand, if the heart continue its normal output, and there be contraction of the arterioles throughout the body, a similar rise in pressure must be brought about. The fact that in certain forms of renal disease (see Chronic Nephritis) there is a widely distributed increase in the fibrous tissue of the arterioles, led to the belief that the renal lesion was secondary to the changes in the arteriole and capillary. There has been a decided tendency of late to include too many conditions under the general head of arteriosclerosis; a recent writer considers aneurysm as one of the manifestations of the disorder.

Calcification of blood-vessels occurs (1) as a result of atheromatous endarteritis or other inflammation of the vessel;

(2) when lime salts are deposited in the vascular wall, without any discernible antecedent disease, the condition is called *cryptogenic calcification.*

Ossification, or true bone formation, is said by Orth to be a possibility; exactly what induces it, or how it may be brought about, is not known.

Hyaline, vitreous, or **diaphanous degeneration,** allied to that form of degeneration described by Zenker as occurring in the muscles, has been found in the vessel-walls, usually in the arterioles. (See p. 246.)

Amyloid infiltration has been considered when dealing with lardaceous disease. (See p. 228.)

Fatty degeneration of the blood-vessels is a disease of the capillaries, the small arteries, and, rarely, the veins. It occurs most commonly in the capillaries of the brain. As to cause, it is observed in connection with (1) old age, (2) pernicious anemia, (3) phosphorus-poisoning, and (4) general debilitating conditions.

The change in the intima resembles the degenerative lesion of atheroma, but is not accompanied by any fibrous tissue formation or other phenomena so constantly associated with atheroma.

Histology.—The vessel-walls are converted into a fatty cellular debris without any preceding inflammatory process like that of atheroma.

An **aneurysm** is a tumor-like sac, containing blood and communicating with an artery. (See Fig. 246, p. 477.)

The *sac* may be made up of one or more coats of the blood-vessel, when it is known as a *true aneurysm—arterial ectasia;* when the sac is formed by the condensed tissues around the vessel, the walls of which have entirely given way, the condition is spoken of as a *false aneurysm.*

Causes of Aneurysm.—Aneurysms are said to be (*1*) *traumatic* or (*2*) *idiopathic.* As nothing occurs without a cause, it would be better to call the latter *cryptogenic.* Further, the causes of aneurysm are said to be (*1*) *predisposing* and (*2*) *exciting.* Of the former, many of the degenerations of the vessel-walls that have been studied, and that weaken the artery, are eminently predisposing; atheroma is doubly dangerous in that it renders the vessel rigid and at the same time weakens the wall. The fact that syphilis favors or often brings about arterial disease or degeneration makes it a predisposing cause of aneurysm. Between the thirtieth and fortieth years of life the arterial changes described in the preceding pages are likely first to evince themselves; the heart is yet in full power, in most individuals, and, with the maintained cardiac force and diminished strength of the

diseased arterial wall, rupture or dilatation of the blood-vessel is likely to ensue. Suddenly developed, powerful cardiac force—such as may occur from a hard lift, sudden spring, or vault—doubles the demand on the semirigid and weakened vessel-walls.

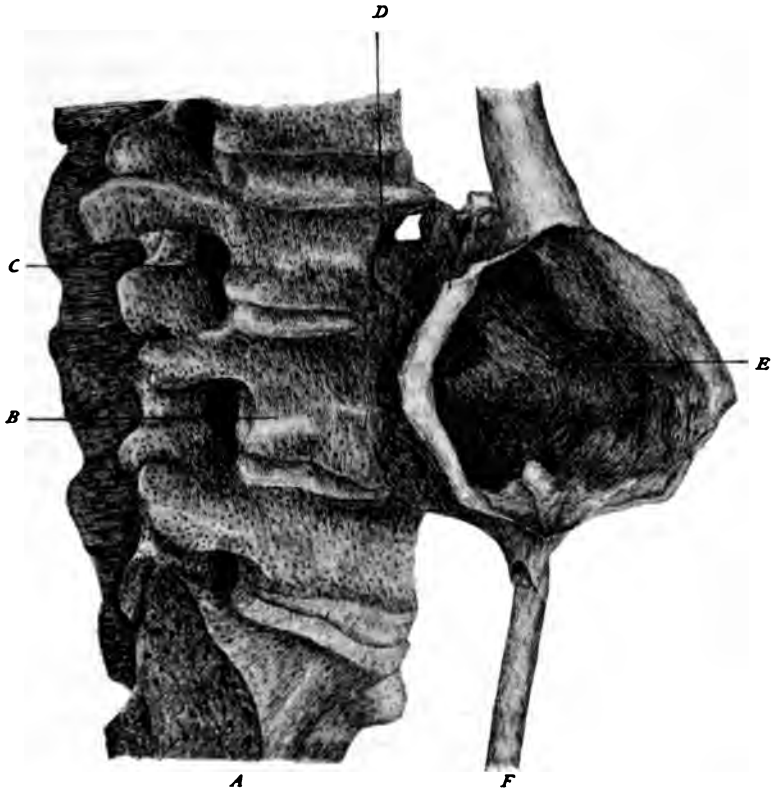


FIG. 257.—SYMMETRIC ANEURYSM OF THE ABDOMINAL AORTA.—(*Specimen in the museum of the Jefferson Medical College.*)

A. Sacrum. *B*. Fourth lumbar vertebra; the anterior part of the body has been eroded by the aneurysm. At the inferior margin calcareous material has been thrown out; anteriorly, this covers the cartilage. *C*. Body of third lumbar vertebra. At *D* the aneurysmal sac has been cut away to show the absorption of the body of the vertebra. *E*. Cavity of the aneurysm. At the lower part of the cavity, between the points of exit of the two iliac arteries, a sharp spicule of a calcareous plaque will be seen projecting upward. *F*. Left iliac artery; the right iliac artery will be seen as a short stump at the lower part of the aneurysmal wall.

The male is more liable to these sudden exertions, and hence aneurysm is much more prevalent in that sex. Injury to the blood-vessel may be an exciting cause or a predisposing element; if the injury be a puncture, it may be followed immediately by a

false aneurysm; a contusion may give rise to arterial changes that weaken the wall and cause it to give way when subjected to a strain that would not influence the normal vessel. Stretching and twisting of vessels, as in dislocations and fractures, or in their reduction, have been followed immediately by aneurysmal dilatation.

Form of Aneurysm.—(*A*) *Classified by the shape:* (*1*) *Cylindric*, uniform distention of the vessel. (*2*) *Fusiform*, or spindle-shaped. (*3*) *Cirsoid*, a number of arteries irregularly dilated. When a single artery is involved, the term *aneurysmal varix* is used. (*4*) *Saccular*, in which a distinct pouch is formed. If on one side of the vessel and communicating by a small opening, it is spoken of as *asymmetric;* if the sac be uniformly distributed around the vessel, as in the miliary aneurysm of the brain, it is *symmetric*. (*5*) *Arteriovenous aneurysm*, where injury has established communication between an artery and a vein. When the wall sharply defines the aneurysm, it is spoken of as *circumscribed;* when the blood cavity terminates in infiltrated tissue, the term *diffuse* is applied.

(*B*) *Classified by the cause:* (*1*) *Traumatic*—an aneurysm arising suddenly, as from an ulcerative endarteritis or trauma, is sometimes spoken of as an *acute aneurysm;* (*2*) *idiopathic* or *cryptogenic;* (*3*) *embolic*, due to proximal distention in occluded vessels, usually terminal; (*4*) *dissecting aneurysm* due to blood dissecting between the layers or coats of a vessel's wall; (*5*) *verminous aneurysm*, one containing a parasite such as is found in the mesentery of the horse.

(*C*) *Classification based on duration and changes in the wall:* (*1*) An *acute aneurysm* or *recent aneurysm* is one quickly developed, and is usually traumatic; (*2*) *chronic* or *old aneurysm*, an aneurysm that has persisted longer, as shown by the changes that its walls have undergone.

Results of Aneurysm.—(1) Disturbance of blood distribution; (2) pressure on surrounding tissues and organs; (3) rupture; (4) cure and arrest of further circulation through the altered vessel.

Cure of Aneurysm.—(1) Clotting or fibrinous deposit must occur; this may be in layers (laminated) (see Fig. 246, p. 477), or it may be a central clot apparently formed as one mass. By occluding the point of exit the circulation is arrested. (2) The coagulum may remain unaltered for years. The writer saw a case in which all symptoms except the presence of the tumor had been absent for eight years, the proximal and distal ends of the vessel having undergone obliterative arteritis. (3) In time, blood-

vessels may permeate the clot and organization of the mass may ensue. (4) The young blood-vessels may dilate and canalization may occur, reestablishing the circulation. (See Canalization of a Thrombus, Fig. 186, p. 273.) (5) A mass of fibrous tissue may remain and mark the site of an aneurysm.

Hypertrophy of Arteries.—When a large arterial trunk is obstructed, the blood supply to the part beyond may be maintained by enlargement of branches, rising above the point of obstruction, and anastomosing with branches from below; the latter may also increase in size. The condition is one apparently of true hypertrophy. The anastomotic circulation eventually becomes as competent to carry on the functions of nutrition as were the normal vessels. When this occurs, it is said that a collateral circulation has been established by anastomosis.

VEINS.

Normal Structure.—Veins have normally the same structure as arteries, except that the tunica media is very much less developed, and hence the walls are thinner. Many of the veins are supplied with valves, and thus differ from the arteries.

Inflammation of Veins (Phlebitis).—Inflammatory processes analogous to those already described as occurring in the arteries take place in the veins, the most important of which are the infective forms—**infectious phlebitis.** As in the veins the current is from the smaller lumen to a larger one, dislodgment occurs, and emboli are thrown off in large numbers. When considering thrombosis and embolism, this point was mentioned. (See p. 267.) The source of the infection in veins may be by (1) direct infection, as in wounds; (2) mural implantation; (3) continuity of spread (that is, passing directly along the vessel-wall); (4) by contiguity, from periphlebitis. As examples of the last two may be cited the spread from infected uterine sinuses to pelvic veins and the extension of suppurative mastoid disease to the adjacent intracranial sinuses respectively. Pyemia and other systemic septic conditions may result.

When the inflammation begins in the intima as a result of extension of an inflammation along the wall, a thrombus commonly follows the progress of the inflammation. In other cases a propagated thrombus invading a vein may give rise to inflammation, justifying the term *thrombophlebitis*. The presence of bacteria in practically all these thrombi is usually admitted; in many of them pyogenic organisms are almost exclusively the cause, and such venous inflammation has received the name *suppurative*

phlebitis. In other cases neither suppuration, softening, disintegration, fragmentation, nor dislodgment occur. The absence of such changes indicates that the condition is not suppurative, but by no means excludes infection, such as typhoid fever, influenza, and, more recently, rheumatism. The simple, bland, or *noninfective phlebitis*, such as follows injury of the vein without infection, is inconsequential, and is usually unattended by secondary processes.

Chronic phlebitis or **phlebosclerosis** is a morbid entity studied by Thoma, who believes it to be part of a general vascular disease (*angiosclerosis*). The wall of the vein, usually immediately beneath the intima, shows a marked increase in the fibrous tissue, which may undergo hyaline degeneration; thrombosis is not infrequently present.

Varicose Veins, or Phlebectasia (Synonyms, *Varix, Varicosity*).—This condition consists of more or less irregular dilatation of the veins; as a rule, associated with alterations in their walls and nutritive changes in the area involved.

FIG. 258.—VARICOSE VEINS OF THE LEG.—(*Gould.*)

Sites.—Veins of the leg and thigh; plexus pampiniformis; hemorrhoidal veins; occasionally, the veins of the abdominal wall, and, rarely, intra-abdominal veins—peri-uterine, renal, or mesenteric.

Causes.—(1) Obstruction to the onward flow of the blood: *e. g.*, tumors of the pelvis, pregnancy, etc., inducing varicosity of the veins of the leg and of the rectum; cirrhosis of the liver, obstructing the veins returning from the alimentary canal; tight garters or other constricting bands are also causes. (2) Diseases of the central organ of circulation, leading to venous stasis. (3) Pulmonary obstruction, leading to stagnation of the blood in the veins. (4) Inflammation of the veins, (*a*) leading to softening of the walls, and thus favoring expansion, and (*b*) obliteration or narrowing of a large vein, such as the femoral, by a thrombus or by contraction, and thereby increasing the intravenous pressure in the vessel beyond the point of obstruction.

Forms.—(1) When the dilatation is regular, symmetric, and not associated with lengthening, the condition is known as *simple dilatation;* (2) when the vein is dilated and tortuous, owing to apparent lengthening as well as to dilatation, it is spoken of as

cirsoid dilatation; (3) when the distention is irregular, saccular, or upon alternate sides, the condition is called *varicose dilatation.*

Results of Phlebectasia.—The slowed circulation, passive congestion, lessens the nutrition of the tissues in the area drained by the vessels involved; as a result of failure to remove effete materials, degenerative or even necrotic processes may ensue; edema may occur; clots may form in the veins; the stretching of the walls usually renders the valves inefficient; as a result of the lowered vitality, slight bruises or superficial excoriations are followed by infection in the diseased area, and extensive ulceration commonly ensues. In the testicle lessened nutrition undoubtedly results, and in some instances this may be followed by atrophy of the organ. In the rectum clotting may occur in the dilated hemorrhoidal veins, and violent inflammatory processes may follow, or the venous mass may ulcerate and bleed, or may, by its size, cause more or less obstruction to the passage of fecal matter.

Tumors of Blood-vessels.—Primary tumors of the blood-vessels are rare. They must be of the connective-tissue series. Sarcomata invade the vessels rapidly, and particularly the veins, by which they not uncommonly spread. The cancers can implicate the vessels only as secondary growths or by direct extension of the growth into the vessel-wall. (For tumors of the blood-vessels, blood-vessel tumors, see Hemangiomata, p. 342.)

Tuberculosis of blood-vessels occurs as a result of the mural implantation of the bacilli or by invasion of the blood-vessel wall by a tubercular process from an adjacent tissue. As a result of studies by Weigert, Weil, Orth, and others, it has been recognized that one of the most frequent causes of miliary tuberculosis is a primary infection of the wall of a vein. Such a lesion may occur in the pulmonary vein as a result of its proximity to active tuberculous glands. In other cases tuberculosis results from mural implantation, as is shown by the occurrence of a distinct tubercular endarteritis, of which about nine cases are on record.

Syphilis of the vascular system has been considered under each condition in which it may occur.

LYMPH-VESSELS.

Nutrition of the tissues is largely maintained by the lymph circulating in the interstices or primitive lymph-spaces; this lymph is derived from the blood-vessels. (See Edema, p. 264.) At first the lymph is free in the reticulum between the cells, the

cavities within which it is lodged being called the *primitive lymph-spaces*. From these lymph-spaces there arise the lymph capillaries, which join to form the lymphatic vessels. The larger lymph-vessels possess walls structurally resembling the walls of blood-vessels. The lymphatic capillaries, or lymph canaliculi, are structurally like the blood capillaries, except that they show great irregularity in diameter, often exhibiting saccular, cylindric, and fusiform dilatations.

Malformations of the lymph-vessels are usually manifested as congenital tumors (*lymphangiomata*), which have been considered elsewhere. (See p. 344.) As in the blood-vessels anomalies of origin and course are occasionally found, so in the lymphatic vessels evidences of abnormal distribution of the channels are sometimes exhibited. Thus, carcinoma of the mamma, which normally invades the axillary glands first, may show initial glandular involvement in the supraclavicular glands, thereby proving that, in some instances, at least, the lymph stream from the breast passes in a direction at variance with the normal.

Obstruction of a lymph-vessel may result from pressure, as when adjacent tumors, aneurysms, and cicatrices collapse its walls; inflammation, thrombosis, tuberculosis, and animal parasites (such, for example, as the filaria) may also occlude its lumen. Cancer spreading by the lymphatics may plug the vessels. The changes resulting from occlusion of a lymph-vessel depend largely upon the importance of the vessel and upon the possibility of collateral anastomoses. The distribution of the lymphatic system commonly affords abundant opportunity for the lymph to pass through some circuitous route when obstructed in its normal course. When passage in this way can not be provided, the resulting obstruction is associated with edema in the area involved. (See Edema, p. 264.) In other cases, either with or without edema, the lymphatic vessels distal to the obstruction dilate. The dilatation may be restricted to a small area, in which case a lymphangioma results, or it may be diffuse, and manifested by the occurrence of small cysts in the area involved. In still other instances, either with or without any of the foregoing conditions, more or less edema, with marked proliferation of the connective tissues, occurs, giving rise to **elephantiasis** and *elephantoid conditions*. Manson's statistics show that in 96.84 per cent. of the cases of elephantiasis the lower extremities are involved; in 5.86 per cent. the upper extremities; and in 2.3 per cent. the scrotum manifests the change. The enormous overgrowth of the connective tissues may be appreciated by the fact that the scrotum sometimes attains a weight of 200 pounds. On

incision, the tissue involved is found to consist largely of white fibrous elements superficially; and deeper, of a "blubbery-looking dropsical tissue." The lymphatic glands of the area involved are commonly enlarged and fibrous.

Occlusion of the thoracic duct affords a slightly different picture by reason of the fact that the vessel contains and transmits chyle. It may be obstructed from the same causes as those already given for lymphatic trunks elsewhere. Thrombosis involving the left innominate vein occludes the duct at the point where it empties its contents into the venous circulation. As in obstruction of other lymph-channels, it is possible to have absolute occlusion of the thoracic duct without any untoward manifestation, in which case the fluid that it normally transmits must enter the circulation through some circuitous route. As a result of obstruction, **chylous ascites** may occur. (See p. 472.) Similar effusions are occasionally observed in the pleural cavities, and **chylocele**—an accumulation in the tunica vaginalis testis—at times follows obstruction to the course of the intra-abdominal lymph. In other cases there is an accumulation of chyle in the lymphatics of the scrotum, constituting so-called **lymph-scrotum**; and in still other instances the obstruction to the onward flow of the lymph is manifested by the occurrence of **chyluria.**

As a result of obstruction to the flow of the chyle along its normal course in the vessels of the mesentery, cysts are occasionally formed. Not infrequently these cysts closely resemble abscesses, for which they have been mistaken. A microscopic or chemic examination of their contents prevents this error in diagnosis. Obstruction to the onward flow of chyle materially interferes with nutrition, leading to more or less anemia, and eventually, in many cases, to emaciation.

Lymphangitis, angioleucitis, or inflammation of the lymphatic vessels occurs in two forms—*acute* and *chronic.*

The acute form is usually due to infection by pyogenic organisms, and is, therefore, most commonly suppurative in character. It may accompany erysipelas or may result from the extension of infections, such as abscesses. The dissection and postmortem wounds of common occurrence and great mortality before the proper injection of anatomic material were typical examples of *acute suppurative lymphangitis.* That acute inflammation of the lymphatic vessels is not always due to bacteria is indicated by the occurrence of a typical form due to filaria, and of another variety, brought about by the introduction of venom into the lymph-spaces. Severe bruises and burns, the former often without any

solution in the continuity of the skin, may be followed by acute lymphangitis.

The morbid anatomy of the condition depends largely upon whether the process is restricted to the lymph-spaces or passes beyond these structures and invades the vessel properly so called. In the former instances (*acute reticular lymphangitis*) there is dilatation of the blood-vessels, giving rise to redness, which often shows a peculiar mottling due to its irregular distribution. More or less edema (swelling) is present. In the *acute tubular lymphangitis* the lines of hyperemia and swelling follow the course of the lymphatic vessels; usually they are broader than the duct, as a result of the presence of an associated *perilymphangitis*, or, rather, a reticular lymphangitis surrounding the inflamed vessel. On microscopic examination, the lymph-spaces will be found to contain numerous leukocytes, and later, in pyogenic infection, the accumulation may be sufficient to justify its being called a distinct pus collection. Fibrin is nearly always present at some stage in the process. In the lymphatic vessels swelling and desquamation of the endothelium occur, associated with more or less marked leukocytic migration, and not infrequently with thrombosis. The extent and termination will depend largely upon the character of the infection and upon the resistance of the individual. In areas of lymphatic obstruction—such as lymph-scrotum and elephantiasis—the absence of sufficient protective powers on the part of the tissues may lead to disastrous infections. In other cases the virulence of the infecting agent may be overwhelming, and associated with the production of poisons that rapidly destroy life, or by the diffusion of bacteria into the lymphatic glands, and eventually into the blood-vessels, septicemia or pyemia may ensue. In still other cases the virulence of the infection may be slight or the resistance of the tissues marked, and in either case the process may quickly subside.

Chronic lymphangitis may follow the acute form or may result from gradually developing obstruction to the onward flow of lymph. It is frequently observed in lymphangiomata. It is manifested by more or less dense edema of the area involved, with proliferation of the connective tissue, leading to a true fibrous induration.

Lymphangiectasis and lymphangioma have been referred to in considering tumors. (See p. 344.) Tumors of the lymph-vessels, aside from those resulting from lymphangiectasis, either congenital or acquired, are usually secondary, and are due to invasion of the adjacent tissues or primitive lymph-spaces. *Endotheliomata* of the serous membranes are usually regarded as primary tumors

arising from the endothelium, and are allied to, if not identical with, similar tumors the origin of which is the endothelium of smaller lymph-spaces or lymph-ducts. The extension of cancer by the lymph-spaces has already been considered. (See p. 319.)

In connection with or independent of associated tuberculosis of the lymph-glands the process may involve the vessels. Extension onward to the nearest glands or to the blood stream is possible. When tuberculosis occurs in the thoracic duct, either as a result of mural implantation of tubercle bacilli, which have found entrance near the periphery of its distribution, or when an adjacent tuberculosis invades the structure, disaster due to systemic dissemination is prone to follow.

CHAPTER VII.

MUCOUS MEMBRANES.

Normal Structure.—A mucous membrane consists essentially of three parts: (1) Upon the surface, a layer of epithelial cells; (2) a basement membrane, upon which these cells rest; (3) the submucous connective tissue, in which ramify the blood-vessels, lymphatics, and nerves essential to the life and functions of the layers above.

1. The *epithelial layer* varies in two particulars: (*a*) in the character of the epithelium and (*b*) in the number of layers. When the function of the epithelium is largely protective in character, it is found in a number of layers; when secretion is the essential function, there is commonly but one layer: *e. g.*, on the tongue numerous layers are found, while in the tubules of the stomach, the acini of glands, and the tubules of the kidney, etc., but a single layer exists. When, in addition to protection, propulsive force is needed, or when the latter alone is demanded, the epithelial cells are supplied with cilia, as in the bronchi, Fallopian tubes, etc. In all mucous membranes possessing a stratified epithelial layer there lies immediately adjacent to the basement membrane a genetic layer analogous to the cylindric-cell layer of the rete mucosum of the skin. When the epithelial covering is simple (nonstratified), a distinct genetic layer may not be demonstrable, as in the vesicular portion of the lung and the tubules of the kidney. Mucous membranes so constructed must, after exfoliation or destruction of a single layer, recoat the connective-tissue basement membrane from the viable cells at the margin of the area involved, exactly as the epithelial regeneration progresses over the surface of an ulcer undergoing repair.

Epithelial cells possess the remarkable faculty of manufacturing from supplied nutrition new chemic compounds not existing, as such, in the pabulum supplied: *e. g.*, the secretions of the salivary glands, the gastric follicles, the pancreas, the kidney, etc. Every mucous surface is, therefore, a laboratory, and this peculiarity has given the membrane the name specialized, indicating that it possesses characters eminently its own. While all mucous membranes elaborate something, the most constant element

is mucus; when altered by disease, it not uncommonly is the sole product of a tissue the function of which is the manufacture of a material to be further utilized by the economy, or the excretion of an agent for which the organism has no further use; and when such perversion of cell activity exists, the evidences are not slow to appear. As the function of the cell is dependent largely upon the pabulum supplied, and as this supply is controlled by the subepithelial layers, it becomes evident that the alteration of the basement membrane or of the submucosa must affect the activity of the superimposed epithelium.

2. *The Basement Membrane* (*Membrana Propria*).—This structure is mesoblastic in origin, composed of fibrous tissue and, in some situations, a scant supply of unstriped muscle-cells. The thickness of the basement membrane varies greatly; thus, in the mouth and nose it is of a discernible thickness, while in the wall of the pulmonary alveoli it is demonstrated with difficulty. When great changes in the volume and surface of the organ are likely to occur, the basement membrane may be thrown up in irregular ridges. By some it is claimed that the nerves and lymphatics penetrate this structure and present themselves immediately in the epithelial layer. It is not, however, probable that such is the case; the basement membrane being the line between the connective and epithelial tissues, it seems extremely probable that it is merely pushed as a thin layer ahead of the nerve-fibers, and that the lymphatics open by stomata immediately beneath or into the genetic layer of epithelium when such exists.

3. The *submucosa*, or submucous connective-tissue layer, is of the greatest importance, and varies more than either of the preceding. In a part of the nasal fossæ it is erectile; where an organ is subject to great alteration in surface, like the stomach, it is especially abundant; where it is not to be called upon for such alterations in surface at such rapid intervals, it may be wanting, as in the uterus, where it is extremely scanty, if present at all. As the nutrition of the epithelium is largely dependent upon the condition of the submucosa, lesions of this layer influence the function and structure of the overlying membrane. In many mucous membranes collections of lymphoid follicles are to be found. For the most part these nodes occupy the submucosa, although in numerous situations the membrana propria contains a quantity of lymphoid tissue. The lymphoid elements may be somewhat diffuse, agminated in nodules, or grouped in patches. In certain infectious processes—for example, typhoid fever—the essential lesion involves, to the greatest degree, the lymphoid elements of the mucous membrane.

DISEASES OF THE MUCOUS MEMBRANE.

Hyperemia may be a physiologic process, as in the increased blood supply sent to the stomach during gastric digestion. (For Pathologic Hyperemia, see Inflammation of the Mucous Membranes.)

Congestion of a mucous surface is dependent upon conditions that interfere with the return or exit of the blood. Congestion is seen in the lungs and upper air-passages and in the alimentary canal, as a result of cardiac disease associated with interference in the onward flow of the blood, and in the stomach and intestinal mucous membranes in obstructive hepatic disease as well. It may or may not be the precursor of inflammation, and its permanency is dependent upon the condition that causes it.

The function of the membrane is materially altered by the faulty metabolism that always attends a stagnant circulation. In time an increase in the fibrous tissue of the submucosa occurs, usually preceded, accompanied, and followed by a catarrhal process manifested in the epithelial layers above. In obstructive diseases of the lungs or heart the congestion of the gastric mucous membrane may be so great as to resemble the lesions resulting from poisoning.

Hemorrhage from the mucous membrane occurs as a physiologic process in menstruation; hyperemia and congestion not uncommonly terminate in hemorrhage, as in yellow fever, congestive malaria, and allied conditions. It is not always an evidence of any serious malady, as is shown by trifling epistaxis without apparent cause. In hemophilia and scurvy epistaxis is a common occurrence. As to severity, the hemorrhage may consist of the trifling escape of a few red corpuscles in an abundant mucous exudate (serosanguineous) or it may be alarming; the escaped blood may pour out on the surface as in epistaxis, or it may infiltrate the submucosa (interstitial or purpuric hemorrhage) and be found postmortem in the intestines or elsewhere as purpuric spots. During life, in purpura, exposed or visible mucous surfaces may exhibit the discolorations in a typical manner. These spots, if large, may give rise to sloughing (gangrene) in very exceptional cases, and, if the patient survive, ulcers may develop, although this is rare; as a rule, if recovery occur, the blood is absorbed without any septic or gangrenous process.

Atrophy of the mucous membrane. (See Inflammation of the Mucous Membranes.)

Hypertrophy of the mucous membrane. (See Inflammation of the Mucous Membranes.)

INFILTRATIONS OF THE MUCOUS MEMBRANES.

Pigmentary Infiltration.—**(A) Pneumoconiosis.**—Solid particles may gain ingress to or through the mucous membrane from the surface, as in laborers whose occupation exposes them to the constant inhalation of suspended solid matters: *e. g.*, the inhalation of coal-dust by laborers in anthracite mines leads to a condition in the lungs known as **anthracosis**; in the grinders of metal instruments, in nailers, etc., iron inhaled leads to an allied condition, known as **siderosis** (when the disease occurs in nailers, it is also known as *nailer's phthisis*); in stone-cutters and the makers of grindstones, etc., the disease is known as **lithosis** or **chalicosis.** Similar infiltrations occur in laborers in cotton

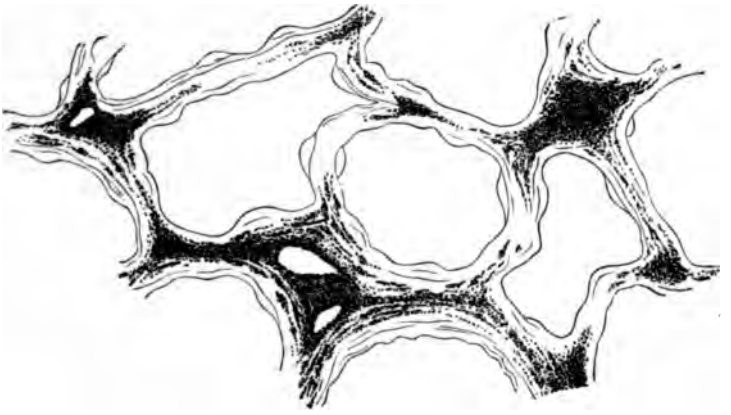


FIG. 259.—SECTION OF THE LUNG, PNEUMOCONIOSIS.—(*Rindfleisch.*)
The deposited pigment is shown in the connective tissue of the vesicular wall.

and shoddy mills and in the handlers of grain. These pigment particles do not seem to be able to penetrate the stratified epithelium, but gain ingress further down in the air-passages; the alveoli being permeable, the epithelial cells not arresting all the pigment, it enters the lymph-spaces of the basement membrane and from there diffuses by the lymphatic channels into the surrounding tissues. The deposited material finds lodgment in the following structures (Hamilton): in the subpleural and interbronchial tissues; in the peribronchial glands; in the lymphadenoid interspaces of the alveoli.

After the disease is well advanced in the pulmonary tissues, the substernal and general mediastinal glands may be infiltrated. Weigert asserts that the circulation may be reached by the pig-

ment passing through the peribronchial glands, which attach themselves to the pulmonary veins, into which they may rupture. The presence of foreign solid material induces inflammation of the mucous covering—at first acute; but from the continued application of the irritant, the changes incident to chronic inflammation occur. In the deeper tissues fibroid hyperplasia ensues, with the abundant production of new fibrous tissue in the infiltrated areas. The catarrhal processes denude the epithelial protecting layer, and the lung tissue becomes exposed to the dangers of

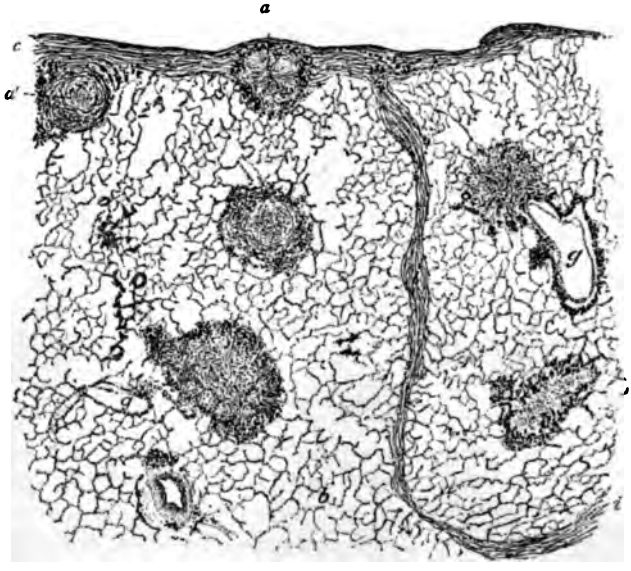


FIG. 260.—SECTION OF LUNG SHOWING CHALICOSIS.—(*Schmaus.*)

a. Collection of infiltrated material lodged in the pleura, *c*. A capsule of fibrous tissue has formed around it. *a'*. Similar nodule in the lung tissue. Other nodules are shown. *b*. Unaffected pulmonary tissue. *c*. Pleura. *g*, *g*. Blood-vessel, around one branch of which a nodule is forming. *i*. Interlobular septum, showing some thickening.

infection by bacteria. Pyogenic organisms lead to infective inflammation and softening in the fibrous areas, and eventually to cavity formation; or, what is much more common in susceptible individuals, tubercular infection terminates the case. Aside from the lung, a similar pigmentary infiltration is occasionally seen in the vomer and turbinated bones.

Occasionally, metallic substances taken as medicines or otherwise may be precipitated in or on the mucous membranes with which they come in contact. Examples of this are seen after

the administration of iron or bismuth. (See Pigmentary Infiltration, p. 231.)

(B) Pigment Deposit from the Blood.—Brown induration of the lung is in part a pigmentary infiltration, secondary to chronic congestion. The disease is most marked in the lung in chronic heart disease. The alveolar epithelium contains altered blood pigment, and pigmented cells are found in the interalveolar wall. The capillaries are distended, and the fibrous tissue of the lung is increased in amount. The lungs, on opening the chest, do not immediately retract; they are at first brownish-red in color, but on exposure to the air they become livid red from the oxidation of the excessive quantity of hemoglobin; as a result of the increase in fibrous tissue the organs are denser than normal, cutting and tearing with considerable resistance.

Deposition of coloring-matter is found in other mucous membranes, where constant or repeated congestions occur, as in malaria; the intestinal, gastric, and hepatic tissues showing the change in the highest degree.

Fatty infiltration seems exceedingly rare, if it ever occurs, in a mucous surface. The author has never seen it. In the glands of the mucosa it may occur, and in the liver it is rather frequent. (See Fatty Infiltration of the Liver.)

Albuminoid or amyloid infiltration, when the general disease is present, invades the mucous membrane (submucous blood-vessels) of the stomach and intestines, rarely the gullet or the air-passages. (See p. 228.)

Calcareous infiltration is usually secondary to chronic inflammatory changes.

DEGENERATIONS OF THE MUCOUS MEMBRANES.

Granular degeneration, or *cloudy swelling*, occurs in the various epithelial structures as the result of high temperature, overwork, or beginning inflammation and necrosis; it is seen to the best advantage in the epithelium of the kidney and liver. (See p. 241.)

Fatty degeneration, or *fatty metamorphosis*, representing, as it does, a later stage of the granular process, will be seen when the latter condition has lasted for any length of time with persistent or progressively increasing causes. It has been noted in pernicious anemia. (See p. 242.)

Coagulation necrosis is a composite degenerative process that occurs in mucous membranes under certain conditions. If the blood supply to an area be cut off, the area dies, if collat-

eral nutrition be insufficient. Fibrin is found matting the elements together, and, later, granular, fatty, and infective changes lead to its absorption, separation, or ulceration; the infective changes, if pyogenic, lead to ulceration or abscess formation, and occasionally, on mucous surfaces, a wide-spread lymphatic infection finds entrance through an area that has undergone coagulation necrosis: *e. g.*, streptococcus-infection of the lymphatics, accompanying or following diphtheria. Coagulation necrosis most commonly is associated with or follows infective processes,

FIG. 261.—GRANULAR DEGENERATION (CLOUDY SWELLING) OF THE LIVER CELLS. —(*Schmaus.*)

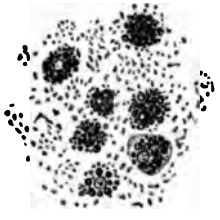


FIG. 262.—FATTY DEGENERATION OF THE LIVER CELLS.—(*Schmaus.*)

FIG. 263.—GRANULAR DEGENERATION OF THE KIDNEY EPITHELIUM (CLOUDY SWELLING).—(*Schmaus.*)

such as typhoid fever, diphtheria, etc., but may result from emboli lodging in the vascular supply of the submucosa, the infarcted area disappearing by coagulation necrosis. By some this process is called a *hyaline* or *fibrinous transformation.*

Coagulation necrosis is also classed with the degenerations, but as it occurs almost exclusively in consequence of inflammation, it is separately considered.

INFLAMMATION OF THE MUCOUS MEMBRANES.

There is probably no tissue in the body so prone to inflammatory processes as the mucous membranes, and as these inflammations occur as the result of many and complex causes, and are modified by the character of the membrane, as well as by its function and by the cause, to describe each anatomic and etiologic form would require more time and space than is allotted to the present volume. For convenience of description the inflammations are divided into the (1) catarrhal, (2) pseudomembranous, (3) hemorrhagic, (4) gangrenous, (5) suppurative, and (6) chronic infectious.

1. **Catarrhal inflammations** are clinically spoken of as (*a*) *acute* and (*b*) *chronic;* pathologically, they occur as more or less acute processes, becoming chronic by prolongation of one stage of the acute; or by repeated attacks changes are induced that are, in many instances, permanent.

(a) **Acute catarrhal inflammation** arises as a result of many complex causes applied from without or exerting their influence from the circulatory side of the membrane. Inflammations of the mucous membrane result most commonly from some form of infection. Nearly all the acute infectious diseases—such as measles, scarlet fever, typhus fever, diphtheria, etc.—are accompanied by, or may incite, a catarrhal inflammation of one or more mucous surfaces; the same is true of the chronic infectious diseases, such as tuberculosis and syphilis, if they occur in the mucous membrane.

The application of other irritants to the mucous surface is, next to infection, the most common cause, and embraces a multitude of subcauses: *e. g.*, foreign bodies; heat, as by hot air, steam, or a liquid such as hot water; irritant gases, as chlorin, bromin, ammonia, sulphurous acid; poisons, such as escharotics like the mineral acids, arsenic, etc., in dilutions too weak actually to destroy the surfaces with which they come in contact. Inflammatory conditions in the mucosæ may also arise from irritants due to chemic changes in foods, whether the irritant be preformed when the food is taken or develop subsequently by fermentation or other change; as examples of these may be mentioned the ptomain poisonings and gastric catarrh due to fermenting food. Alcohol is also a cause.

While rapid thermic and barometric changes and excessive humidity are alleged causes, they probably act by altering the secretion or circulation, or both, thereby lessening the normal resistance to infection; it is not improbable that many of the previously given causes act in similar manner. Pure mycoses of the mucous surfaces may incite a catarrhal inflammation, often violent in character; as an example of a mycotic infection, apparently restricted to the mucous membrane, thrush is most frequently cited. Bright's disease, rheumatism, gout, and allied diseases may be causes or predisposing factors. The young and the aged seem more susceptible to diseases of the mucous membranes than those in middle life.

While it is not assumed that the foregoing include all the causes, the great majority may be embraced under some of them. All inflammations of the mucous membranes are accompanied by

a catarrhal element, just as all cutaneous inflammations are associated with some tendency to desquamation.

Morbid Anatomy.—In the first stage of the inflammation the surface is dry, or is lightly covered by a thick, sticky, adherent mucus; during life hyperemia is shown by the intense redness, which, in violent cases, may assume a dusky red; a little later will be added evident submucous edema, from the pouring out of serum in the submucosa. The histologic changes of this stage are engorgement of the submucous vessels and infiltration of the submucosa with serum and leukocytes; the epithelium is cloudy, swollen, and desquamating. The morbid physiology is shown in excessive dryness, giving rise, in the vocal organs, to the husky, rough voice or to a cough; in the nose, to the "stopped-up" feeling, which is intensified by the erectile tissue becoming far more distended by blood than the ordinary submucosa; in the stomach, the absence of secretion causes anorexia and nausea; in the intestines, constipation, etc.

Immediately following the first or dry stage—which may be brief or prolonged, rarely the latter—an abundant secretion of mucus occurs. The epithelial cells desquamate with the greatest rapidity, and the surface, instead of being dry and sticky, becomes flooded with mucus. The rapidly desquamating cells undergo fatty degeneration and desquamation with such promptness that the special secretion of the part is not elaborated: *e. g.*, in the stomach, pepsin production is arrested; in the salivary glands, there is a lessened output of digestive ferment, and the production of mucus is excessive. The mucous membrane may fail to produce, even in small quantities, the agent which normally it is the function of the mucosæ to elaborate; the apepsia of gastritis may be taken as an example. The inflammatory mucus is composed of the debris resulting from the degenerating cells, a varying quantity of serum, epithelial cells, free nuclei, and leukocytes; more or less of the serum infiltrating the submucosa may osmose through the basement membrane, and may be sufficient in quantity to justify the inflammation being called *serous;* in very severe cases a few red blood-corpuscles escape.

The patient is usually relieved, the submucous circulation being reestablished and the perivascular exudate finding some exit by the surface and the lymphatics. If the cause be now withdrawn, the circulation gradually returns to the normal, absorption of the submucous exudate is completed, and restoration of the epithelial covering from the genetic layer of the basement membrane gradually takes place. Ulceration rarely occurs. The basement membrane is probably never destroyed by a simple catarrhal pro-

cess; when such destruction results, it is most likely that, during the hyperemic stage, stasis occurred in some of the vascular twigs and an ulcer followed by the process of coagulation necrosis.

(b) **Chronic catarrhal inflammation** of a mucous membrane results from the continuance of the last stage of the acute condition or eventually persists after a succession of acute attacks. The chronic inflammations are due to more persistent causes, usually acting from within the body: *e. g.*, the slowed circulation of chronic heart disease, the vascular and blood changes of Bright's disease, gout, rheumatism, malaria, chronic alcoholism, etc., by weakening the resistance of the mucous surface, favor repeated attacks of infection or the persistence of a single attack once developed. The continued presence of irritants also favors the process, as in the forms of pneumoconiosis already mentioned; repeated libations also weaken the mucous membrane.

Morbid Anatomy.—The continued infiltration of the submucosa with leukocytes and serum leads to permanent alterations in tissue; the leukocytes and fixed connective-tissue cells proliferate and form embryonic tissue, and this, organizing into fibrous tissue and contracting, alters the nutrition of the submucosa so that proper functional activity of the epithelial surface is more or less permanently impaired. During the earlier stages the superabundance of the submucous inflammatory products gives the membrane an appearance of thickening, and is often spoken of as an evidence of hypertrophy, or the inflammation is said to be *hypertrophic;* the persistent softened condition of the tube may favor dilatation in this stage. Occasionally, from obstruction of ducts, mucous glands and follicles—as in the mouth, pharynx, and trachea—become distended and prominent. The prominence of these structures has given to the process the name *follicular inflammation.*

As the inflammatory process advances,—grows older,—contraction of the newly formed submucous tissue ensues, leading to lessened blood supply to the surface and to faulty or perverted function of the mucous membrane, associated with thinning—an atrophy, giving the present stage the name *atrophic inflammation;* by reason of the absence or diminution in secretion the process has been called *dry catarrh.* The hypertrophic and atrophic stages of the inflammation may be seen in the same subject at the same time, or the atrophy may be observed to follow the chronic inflammation without the development of very marked thickening, contraction exceeding in rapidity the process of infiltration. Whatever may have been the cause of the inflam-

mation, the bacteria of decomposition find lodgment in the dry and slowly removed secretion, and fetid or poisonous products are developed. This is illustrated in *ozena* and in neglected chronic inflammations of the ear.

Sites.—Catarrhal inflammation may occur on any mucous membrane. Of course, the accident of location gives rise to differences in the character of the lesion, but the essential phenomena will be but variations of the stages and processes indicated. The site and name for some of the accompanying catarrhal

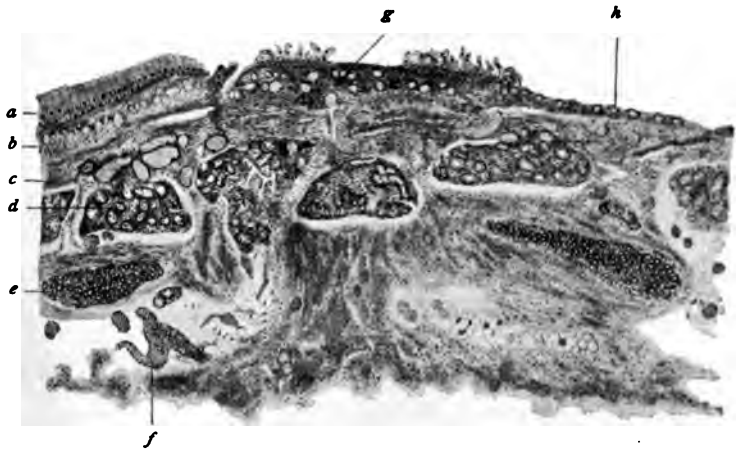


FIG. 264.—SECTION OF WALL OF BRONCHUS, CHRONIC BRONCHITIS.

Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. (From slide loaned author by Professor Harris.) *a*. Diagrammatic representation of the normal cylindric cells arranged normally. *b*. The line runs just under the membrana propria into a mass of newly formed fibrous tissue, which extends downward to *c*. Just beyond the line from *c* are several blood-vessels distended by blood. *d*. Mucous gland surrounded by considerable fibroid thickening of the submucosa. *e*. Cartilage. *f*. Distended blood-vessel. *g*. Part of the chronically inflamed mucosa, showing inflammatory exudate and progressive fibrosis of the submucosa. The normal cylindric cells that should cover the area are seen to be advancedly degenerated and desquamated, and those remaining are fragmented. To the left of the lower end of the line from *g* (1.5 cm.) is a depression which marks the exit point of a duct from one of the mucous glands. *h*. Denuded surface of the mucosa. Under this point the more recent inflammatory changes are less marked than at *g*. (¼-inch objective, 1-inch ocular.)

processes are as follows: Nose, *rhinitis;* mouth, *stomatitis;* tongue, *glossitis;* tonsils, *tonsillitis;* pharynx, *pharyngitis;* trachea, *trachitis* or *tracheitis;* bronchus or bronchi, *bronchitis;* in the capillary bronchi and the air vesicles, *catarrhal pneumonia* (a condition in which the catarrhal inflammation differs from that observed in other localities in the tendency to accumulation, in changes in the inflammatory products, and in other phenomena, which demand that the process be considered more in detail, as will be done when the forms of pneumonia are described); esophagus, *esophagitis;*

stomach, *gastritis*, or, on account of the symptoms of indigestion, *dyspepsia;* ileum, *ileitis;* colon, *colitis;* ileum and colon, *ileocolitis;* rectum and mucous surface of the anus, *proctitis;* urethra, *urethritis* (when due to the gonococcus and involving the urethra, the process is called *gonorrhea;* the same cause acting on other mucosæ produces what is termed *gonorrheal inflammation*); bladder, *cystitis;* ureter, *ureteritis;* pelvis of the kidney, *pyelitis;* gall-bladder, *cholecystitis;* biliary ducts, *cholangitis.* Catarrhal inflammation occurs, no doubt, in the hepatic structure, but here, as in the lung and kidney, other associated phenomena demand that the condition be considered separately.

2. Pseudomembranous, Fibrinous, Plastic, or Croupous Inflammation.—Of the many names given to this condition, the first-mentioned is to be preferred. The process consists of an inflammation, attended by the development, on the surface of the mucous membrane, of a false or pseudomembrane composed of a solid or semisolid matrix and entangled cell elements.

Causes.—That it can be induced without the intervention of bacteria is established, but that such is often the case is extremely doubtful. Heat, irritant gases, such as chlorin and ammonia, escharotics, which do not destroy the basement membrane, and allied agents, may possibly induce an inflammation attended by the development of false membrane. The local application of lactic acid and other medicaments has led to pseudomembrane formation. Of the many alleged microbic causes, two are established: (1) the bacillus of diphtheria and (2) a streptococcus identical morphologically to that found in suppuration and erysipelas. The pneumococcus has also been found as the only demonstrable organism present. Investigation into the cause of pseudomembranous rhinitis, which often lasts for months, has demonstrated, in a large percentage of the cases, the presence of the bacillus diphtheriæ. It would, therefore, appear that the chronic as well as the acute pseudomembranous inflammation may be, in some cases, at least, due to the Klebs-Löffler bacillus. Pseudomembranous inflammation of the intestine has been observed in pyemia and allied septic conditions; also in pneumonia and typhoid fever, as well as in Bright's disease, cirrhosis of the liver, and cancer (Osler). The same writer has observed membranous bronchitis in pulmonary tuberculosis, and describes a fibrinous bronchitis that arises independent of any known cause.

Morbid Anatomy.—Two forms are recognized—an acute and a chronic; so far as known, the histology and process of development differ only in the chronic form occupying more time.

Of necessity, the process begins as a catarrhal inflammation, with hyperemia and infiltration of the submucosa; liquor sanguinis passes through the basement membrane, and, reaching the surface, the necessary ferment is supplied by the bacteria or the epithelial cells (probably the latter, as the bacteria may be introduced

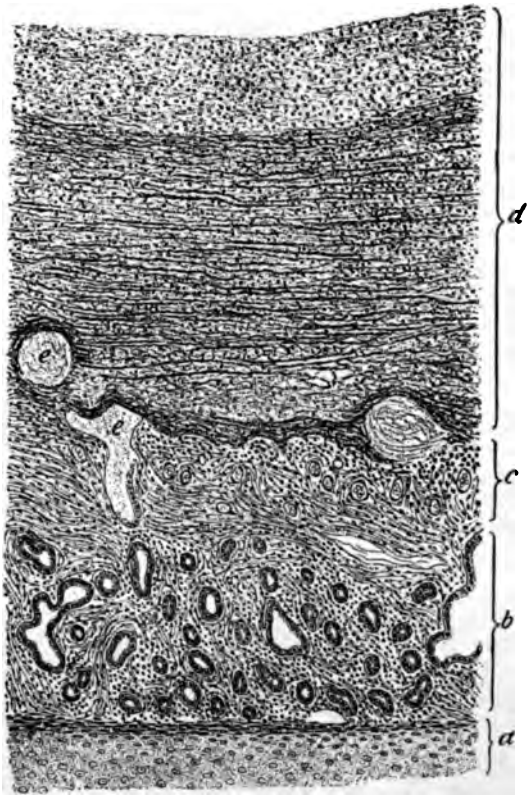


FIG. 265.—VERTICAL SECTION THROUGH THE PSEUDOMEMBRANE AND PART OF THE WALL OF THE LARYNX IN PSEUDOMEMBRANOUS LARYNGITIS.—(*Schmaus.*)

a. Cartilage. *b*. Submucosa, rich in glandular elements, also swollen and with some lymphoid-cell exudate. *c*. Line of the membrana propria. *d*. Pseudomembrane made up of fibrinous elements, in which are entangled leukocytes and desquamated fragmented epithelial cells. *e*, *e*. Gland-duct.

into the circulation of an animal without immediate coagulation of the blood), and coagulation occurs. That all pseudomembranous processes are due to the deposition of a fibrin-forming body has been strongly controverted. It has been shown that the membrane contains mucin, and that it often fails to give the charac-

teristic stain reaction (p. 251) of fibrin. It must not be forgotten that on various mucosæ rapid alteration in the fibrin may occur, and that digestive or like changes may rob it of its specific stain reactions. The fact that mucin is present in the membrane is not astonishing when the frequent entanglement of epithelial cells containing this body is considered. Still, it must be admitted that, with the tests at our disposal, membranes apparently mucigenous and failing to give the fibrin reactions often occur; that fibrin had no part in their formation is not so easily established.

The membrane may be fibrillar,—that is, the fibrin coagulated in fibrillæ, or branching lines,—or the result of the coagulation may be a hyaline, homogeneous film, almost, if not quite, imperceptible. If the exudate be fibrillar, the membrane is clearly discernible during life; if hyaline, it may be quite invisible, even in the throat. Intermediate between the fibrillar and hyaline forms of the membrane is a finely granular deposit, resembling to a certain extent fragmented cells rather than a distinct fibrinous product. The hyaline and granular forms of the membrane—particularly the hyaline—resemble in stain reactions the mucin-containing bodies. The membrane may be laminated, especially in chronic cases; two, three, or even four distinct layers may be shown on section. Sometimes these layers do not adhere to one another and may be separated or separable; the lamination is probably due to a layer of membrane forming, followed by a pause, in which mucus forms below, and then a second layer of membrane forms and another layer of mucus, and so on, until the cavity is freed of, or is filled by, the rapidly forming exudate.

Occasionally, a rather extraordinary periodicity is observed in the appearance of the membrane; this is especially true of the chronic form, in which, exclusive of the pseudomembranous processes that may accompany menstruation, the membrane appears once each week, once each month, or at almost stated intervals. Its appearance may be attended by fever or other symptoms; in the acute pseudomembranous inflammations this always occurs, but in the chronic types no symptoms, except the extension of the membrane, may precede, accompany, or follow its formation. At times a few red blood-cells may be found in the membrane. Exfoliation or casting-off of the membrane may occur as rapidly as it forms, or it may remain and be pushed off by developing mucus or demanded functional activity. When removed, the surface of the basement membrane is exposed; but that tissue is not destroyed, so that the pseudomembrane may be immediately reproduced, or, if the process be in a condition to terminate, the cause withdrawn, a catarrhal inflammation of the mucous surface

ensues, and recovery follows exactly as in simple acute catarrhal inflammations. The tendency to redevelopment of the membrane in chronic cases is manifested by repeated attacks, as in membranous endometritis and membranous proctitis. Of the

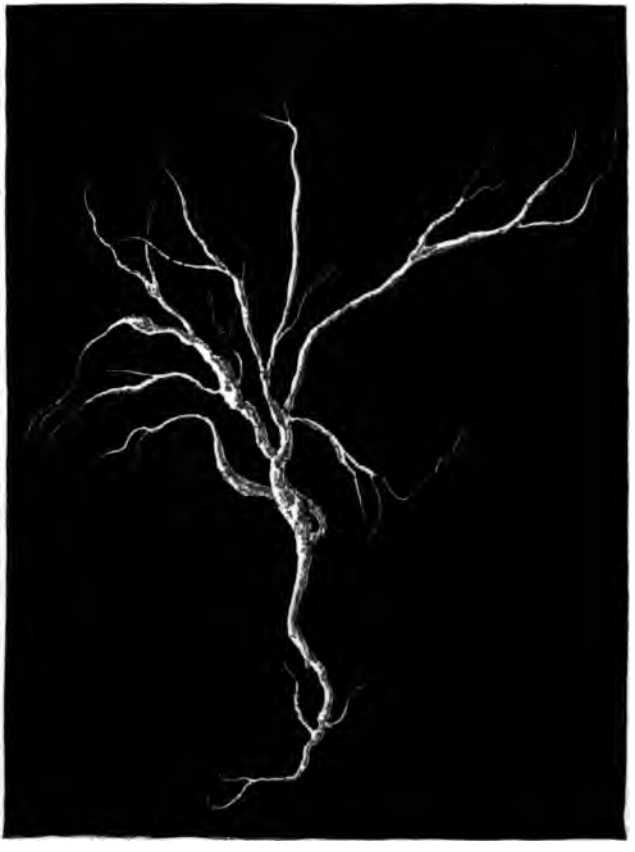


FIG. 266.—FIBRINOUS CAST FROM THE BRONCHI, CASE OF CROUPOUS PNEUMONIA.* —(*Schmaus.*)

chronic form occurring in the bronchi Osler says, "We know of nothing which can prevent recurrent attacks."

Sites.—There is no anatomic reason why pseudomembrane should not occur wherever catarrhal inflammation may develop.

* Pneumonia is not a frequent cause of fibrinous bronchitis.

The acute pseudomembranous process is most frequent in the larynx, throat and nose, intestine, rectum, and middle ear, in the order named ; the chronic form is most common in the uterus, rectum, bronchi, nose, and intestine, in the order given.

3. **Hemorrhagic inflammation** is not common on mucous surfaces. It accompanies intense infective processes, such as pyemia and septicemia, and specific blood mycoses, such as anthrax ; it is not infrequent in violent intoxications, such as occur in fulminating septic peritonitis secondary to a perforation in the alimentary canal (perforating gastric and duodenal ulcers) ; it may follow the application of escharotics, such as carbolic acid, etc.

Morbid Anatomy.—There occurs a violent hyperemia of the mucous surface, attended by interstitial hemorrhage and plugging of the entire capillary area involved ; there may be hemorrhage on the surface of the membrane or into the inclosed cavity. In all cases that have come to the author's knowledge death from other causes must have ensued, the present process being no doubt an important factor in hastening the fatal issue. Should the area involved be small, it is probable that the process could terminate in the gangrenous form. The stomach and intestine are most commonly involved when the accompanying septic process is in the peritoneum. The presence of a similar condition is recognized in diphtheria, and occasionally in smallpox, occurring in the throat, trachea, nose, or mouth. The condition differs from the simple purpuric interstitial hemorrhage in that the latter, if recovery takes place, is absorbed in most cases without destruction or cicatrization of the mucous surface, while in the hemorrhagic inflammation destruction invariably occurs and a scar usually forms to mark the site of the past process.

4. **Gangrenous inflammation** occurs as a result of the hemorrhagic process, or may arise from the same causes. It probably most commonly accompanies diphtheria, and hence at one time was known as *diphtheric inflammation*, in contrast to the pseudomembranous or croupous inflammation—diphtheria and croup being assumed to be different diseases. We now know that the bacillus diphtheriæ may cause both, and other inflammatory processes as well. The *gangrenous sore throat* and *gangrene of the fauces* of the older writers, were types of this inflammation, and were most likely cases of diphtheria. Gangrenous inflammation also follows burns, scalds, escharotic injury, and trauma of the mucous surface. Embolic cutting-off of the blood supply to an area of the mucous membrane may lead to gangrene. The author saw a most extensive gangrenous proctitis

follow the continuous use of opium and morphin in a patient who used three to six grams of the latter each day by rectal suppository. , Administration of mercury, antimony, or arsenic has been followed by gangrenous processes involving the mucous surfaces.

It is probable that *cancrum oris*, *noma*, or *gangrenous stomatitis* is due to a bacteritic factor, although Lingard's bacillus is not generally believed to be the cause. (See Diseases of the

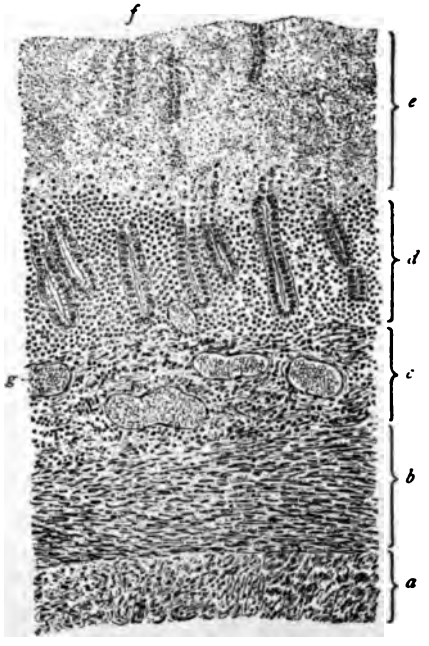


FIG. 267. — VERTICAL SECTION OF MUCOUS MEMBRANE, SHOWING DIPHTHERIC OR GANGRENOUS INFLAMMATION, FROM A CASE OF DYSENTERY.—(*Schmaus.*) × 40 diameters (?).
a, *b*. Muscular layers. *c*. Submucosa with widely distended blood-vessels, swelling, and leukocytic infiltration. *d*. Adherent portion of the mucosa in which degenerative and necrotic changes are in progress, and which fades off into *e*, the necrotic layer of the mucosa. *f*. Part of a gland in the necrotic tissue, the structure of the gland elements not having been, as yet, destroyed, although separating with the necrosed layer. *g*. Distended blood-vessel.

Alimentary Canal; also Gangrene, p. 255.) This disease occurs in debilitated children, and usually follows one of the acute infectious diseases, and most commonly (fifty per cent. of the cases) measles.

The necrotic processes affecting the mucosæ and due to infection by the streptococcus, or, less frequently, the pneumococcus, occasionally manifest a clearly gangrenous tendency. In tissues

weakened by any associated lesion, and often when reduced resistance is not demonstrable, other bacteria, as the colon bacillus, typhoid bacillus, and the staphylococci may give rise to gangrenous processes.

Morbid Anatomy.—Whether the initial cause be infection or not, the circulation is arrested in the area involved, and coagulation necrosis and gangrene ensue; infection (primary, secondary, or multiple) is now assured, and breaking-down follows. As the necrotic area extends into the submucosa to a varying depth, the lymphatic system is widely opened and absorption of microbic poisons follows, with all the phenomena of grave septic intoxication. The plugs that occlude the vessels become infected and break down, and hemorrhage may result; or bacteria (most commonly streptococci) gain ingress to the lymphatic system, and enlargement, and even abscess formation, in the nearest lymphatic gland may follow; or, bacteria reaching the blood, may give rise to septicemia. The gangrene may assume phagedenic characters, followed by wide-spread destruction; this is probably due to a secondary infection, although, of course, it may have been primary, and is typified in noma—gangrenous inflammation of the labia in the female, and of the glans penis in the male. The initial process in the latter cases may have been a chancre or a chancroid.

Sites.—Gangrenous inflammation is most common in the tonsils, pharynx, mouth, external genital organs, rectum, and colon, but is not infrequent on other membranes as well. The author has observed a severe gangrenous cystitis that followed prostatic abscess with urinary infiltration.

5. Suppurative and pustular inflammations occur on the mucous membranes in pyemia, septicemia, smallpox, and, rarely, in other infectious febrile processes. Erysipelas of the mucous membrane may be followed by suppuration. Diphtheria may, by rendering mixed infection possible, give rise to pus formation in the submucosa. Pyogenic infection of the submucosa results from abrasion or destruction of the protective epithelium, or from the accumulation of infective material in a mucous gland with obstructed duct; the basement membrane of the gland being less resistant than the overlying tissues, rupture of the distended gland into the submucosa leads to infection and pus-formation. This is probably the process giving rise to suppurative tonsillitis and allied conditions.

Abscess in the submucosa of the urethra may follow or accompany gonorrhea. Pus, being a connective-tissue product, develops in the submucosa, and secures egress, if left alone, by rupture, through gangrene or other necrotic process involving

the basement membrane. Dissemination of the poison may occur through the lymphatics, as already stated when considering Gangrenous Inflammation.

Suppurative processes are usually situated in localities liable to injury and accompanying infection, or in membranes rich in sulci affording lodgment for materials that subsequently lead to infection; aside from the specific diseases, such as smallpox, in which the suppuration occurs in the form of pustules in the mouth and adjacent membranes, the most common sites are in the rectum and the appendix. In the latter the infection and pus-formation in the submucosa may find less resistance to egress toward the peritoneum than the mucous tract, and hence appendicitis not uncommonly gives rise to infection of the peritoneum. Similar obstructive conditions may occur in the Fallopian tubes, and rupture into the peritoneum may afford a more favorable route for the infection and emptying of the distended tube than escape into the uterine cavity. While the foregoing reference to appendicular and Fallopian disease is made under Suppurative Inflammation, it is not to be forgotten that accumulated catarrhal material contains abundant infectious agents, and that its escape will be as certainly followed by septic inflammation as though an abscess had poured its contents into the serous cavity. Suppurative and gangrenous processes are not uncommon in the appendix, and it does not seem probable that the Fallopian tube, once infected, should be less liable to the same processes.

6. Chronic infectious inflammations of the mucous membranes are of the greatest importance, and deserve the closest study. For the most part they, from the beginning, involve the essential function of the mucous surface by invading the submucosa. Included under this head are tuberculosis, leprosy, syphilis, glanders, actinomycosis, and rhinoscleroma.

Tuberculosis of the mucous membranes, independent of pulmonary tuberculosis, is not a rare condition. In the upper air-passages it is a most frequent occurrence in tubercular patients, arising in the larynx, in the bronchi, and occasionally in the nose. Tuberculosis of the alimentary canal has been noted in every structure from the lips to the anus. The cause is the bacillus of tuberculosis, which has been considered in the section on Bacteriology. (See p. 180.)

Morbid Anatomy.—Miliary tubercles develop in the submucosa —as a rule, around a blood-vessel; and in marked cases of general miliary tuberculosis the tubercles can be seen at many points in the mucous membrane. A little later these tubercles coalesce and, by the obliterative changes induced in the blood sup-

ply, cut off the nutrition to the basement membrane and epithelium above; by this time, through confluence, necrosis, and softening, a cheesy area develops, and with the breaking of the basement membrane the caseous material is discharged and an ulcer results. The long axis of the ulcer is usually transverse to the long axis of the membranous tube—a condition due to the blood-vessels being distributed circumferentially rather than longitudinally. External to the area of ulceration new fibrous tissue develops and contracts in many localities, giving rise to

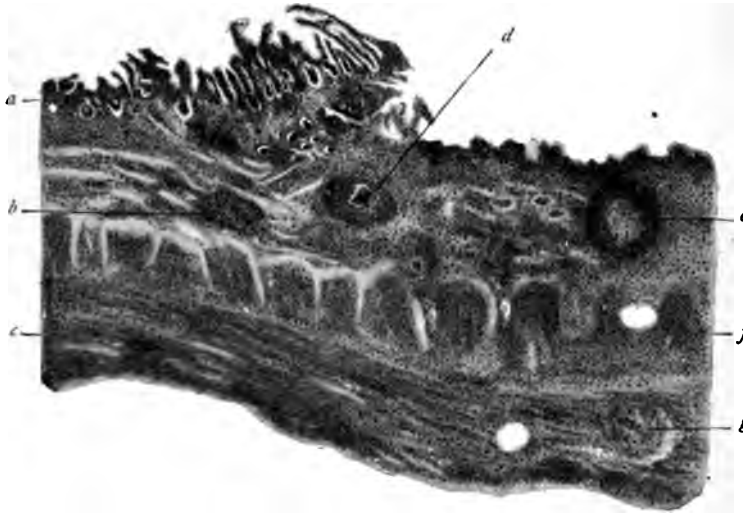


FIG. 268.—MARGIN OF TUBERCULAR ULCER OF THE INTESTINE.

Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a*. Mucosa that, as it approaches the ulcer, is swollen and thickened, with fragmented and desquamating cells. *b*, *d*, and *e*. Tubercles situated in the submucosa; *b* and *d*, and a tubercle just under and to the right of *d*, each show a central giant cell. The tubercle *e* shows central softening and beginning caseation. Note the extensive infiltration of the submucosa with small lymphoid cells, which, immediately under the ulcer, at *f*, have invaded the circular muscle-fibers. *c*. The longitudinal muscular layer, which, at *g*, contains a solitary tubercle. (⅙-inch objective; 1-inch ocular.)

stenoses. When examined in its earlier stages, the condition is known as miliary tuberculosis; and later, when ulceration has ensued, or in the stage of caseation, as ulcerative or caseous tuberculosis, respectively. Rarely, calcareous changes may occur and, as a result of infiltration with lime salts, the tubercle becomes quiescent, the process being arrested. The anatomy of tubercles, their method of infection, etc., have been considered with tuberculosis in general. (See Tuberculosis, p. 366; also tuberculosis of

the various mucosæ and organs—alimentary canal, respiratory apparatus, liver, kidney, etc.)

Leprosy of the Mucous Membranes.—In purely anesthetic leprosy the only involvement noted by observers is in the colon, where ulcers are said to develop without leprous tubercles. Tubercular leprosy is prone to attack the mucous membranes, especially the conjunctiva, cornea, larynx, and nose. The leprous tubercles, like those of tuberculosis, occur in the submucosa and around the blood-vessels; as the process extends, the blood supply is cut off by the obliterative changes in the vessels, and a fibroid area may result. Ulceration is not inevitable, or even frequent, as in the tubercle. Sometimes, however, the leprous infiltration is followed by pyogenic infection, softening, and ulceration. The disease is due to the bacillus lepræ, which has been considered when dealing with bacteria. (See p. 188.) (For pathology of leprosy see p. 379.)

Syphilis of the Mucous Membranes.—In primary syphilis the lesion is far more frequent in the mucous membrane than in the skin. The submucosa becomes infiltrated with small round cells, in which epithelioid and giant cells may be found; the blood supply to the surface is cut off by obliterative changes in the arteries, and ulceration, or rather coagulation necrosis, ensues. The roseolar rashes of the secondary stage leave no discernible lesion. The mucous patches and ulcers are the result of coagulation or liquefaction necrosis, and occur in the mucosa of the tongue, pharynx, tonsils, palate, gums, and cheeks, and also on the mucous membrane of the anus and genital organs.

The lesion of tertiary syphilis affecting the mucous membranes is the gumma occurring in the submucosa, developing like the previously considered infective granulomata, and, when untreated, usually breaking down and ulcerating. As the ulcer heals, contracting cicatrices give rise to strictures; these are most commonly seen in the larynx, rectum, and esophagus. (See illustrations of syphilitic stenosis of the larynx and trachea, Fig. 271, chap. VIII.) Should cicatrization occur, without ulceration, contraction is equally sure to follow, but is less obstinate. (For pathology of syphilis see p. 363.)

Glanders.—This disease, due to the bacillus mallei (p. 179), manifests itself usually in the nose as ulcers brought about by the development of glanders nodules, made up of lymphoid and epithelioid cells in the submucosa, which, breaking down, give rise to an ulcer. In the acute form gangrenous and septic phenomena not uncommonly accompany the process; in the chronic form

the ulcers may be mistaken for those due to protracted catarrhal, tuberculous, or syphilitic disease. The finding of the bacillus is essential to an accurate diagnosis. (For pathology of glanders see p. 375.)

Actinomycosis is most common in the walls of the oral cavity, and is due to the ray fungus or actinomyces (p. 160), entrance being brought about by food containing the parasite coming in contact with an abrasion in the mucous surface. A granulation tumor develops; this is made up of structures resembling, in a crude way, the tubercle. The new formation is usually surrounded by a zone of proliferating connective tissue, which, in the jaw, has been mistaken for sarcoma. Sooner or later suppuration ensues. The diagnosis can be made only by finding the fungus in the tissues or discharges. (For pathology of actinomycosis see p. 377.)

Rhinoscleroma consists in the thickening and tumefaction of the submucosa of the nose, rarely extending to the pharynx or larynx. The tumefaction usually begins in the nose. The tumefied areas are at first red or pink, and are very tender; later they become white. The disease is due to a bacillus (see p. 178) found in the tumefied area, usually in the hyaline cells of the fibrous meshwork. The disease is rare in this country, and clinically resembles lupus. It is essentially chronic as to time, requiring years fully to develop.

The tumors, which may occur on or in mucous membranes, are numerous, and, as certain localities seem liable to given tumors, it is thought best to record the neoplasms and cysts with the special pathology of each region.

CHAPTER VIII.

ORGANS OF RESPIRATION.

Anatomic Divisions.—From an anatomic standpoint the organs of respiration are divided into the *nose* or *nasal cavities*, *larynx*, *trachea*, *bronchi*, and *lungs*. For physiologic consideration these are divided into the conducting part, including all but the lungs, in which the essential chemistry and vital phenomena of respiration occur. Incidentally, other functions are performed by the various parts of the whole, one function being accessory to another,—*e. g.*, olfaction in the nose, vocalization, etc., in the larynx,—all aided by and dependent upon the various muscular and bony structures of the chest with its complex innervation.

NOSE.

Malformations.—The nose may be absent or may be represented by a teat or a snout-like projection in *cyclopia* or *synophthalmia*—a malformation attended by a single orbital cavity, centrally located, and containing one or two eyeballs in varying stages of development; rarely, no eye may be present. Other malformations of the nose consist in absence of one or more muscles, clefts of the alæ, deviations and faulty development of the septum, incomplete development of some of the bones entering into the formation of the cavity, constriction of the nares, more or less complete, and clefts in the floor of the nasal cavity, usually associated with faulty development of the lip, palate, or other soft parts. (See Malformations of the Mouth.)

Hemorrhage from the nose (epistaxis) occurs as the result of injury, either directly applied to the nasal structures, or falls and blows severely jarring the head; fractures involving the base of the skull; extreme plethora is asserted to be a cause; hyperemia, either premonitory to inflammation or secondary to overexertion and forcible cardiac action, may be a cause; violent respiratory acts, like strangling, coughing, or sneezing; intracranial congestion and hyperemia; in the passive congestions of heart disease and obstructed return of blood from the head, as in tumors pressing on the veins of the neck; occasionally the hemorrhage is vicarious, as in arrested menstruation and suspended

excretion (*e. g.*, sweating and suppression of urine); severe vomiting may cause it; tumors, ulcerations, etc., of the nasal mucosa; blood diseases, like hemophilia, scurvy, leukemia, etc. Epistaxis is also seen in the early stages of some of the acute infectious diseases, most commonly typhoid fever. Renal disease, associated with a rise in blood pressure, and cirrhosis of the liver are also causes. Death from epistaxis is rare. The quantity of blood lost varies, but usually stops short of danger. When bleeding is repeated, there is not infrequently some local lesion to account for it, such as erosion or ulceration, most commonly situated on the septum. Varicosity of the veins of the nasal mucosa may sometimes be recognized.

Inflammation of the nasal mucosa is spoken of as **rhinitis.** (For pathology of acute and chronic forms of inflammation and changes in inflammation of the mucous membranes see chap. VII, part III, p. 536.) Any of the already described mucous membrane inflammations may occur in the nose. The acute catarrhal inflammation—*acute catarrhal rhinitis, acute nasal catarrh, coryza*—is the most common. Of the many conditions believed to be operative in the production of acute catarrhal rhinitis, infection must be presumed to be predominant. Cold and exposure, irritants, such as ammonia, and superheated gases are said to be etiologic factors. Cold and exposure are practically of secondary importance, probably only increasing the liability to infection. There is, at times, evidence that might lead to the belief that the condition is contagious. The inflammatory process secondary to infectious diseases, such as influenza and typhoid fever, merits nothing more than mention.

Fibrinous and gangrenous inflammations of the nose may be primary, but are more frequently associated with or secondary to a primary pharyngeal lesion. *Pseudomembranous rhinitis* is, in a certain percentage of cases, a nasal manifestation of diphtheria. This statement applies not only to the acute forms, but to the more chronic cases as well. Some of the latter show a persistent, rather long-continued pseudomembranous inflammation; the diphtheria bacillus is present in the exudate, and, in rare instances, may constitute the starting-point for an epidemic of diphtheria. Pseudomembranous rhinitis from other causes occurs, but is infrequent. *Chronic nasal catarrh* usually follows repeated acute attacks of acute inflammation, although occasionally it comes on insidiously and may induce lesions of considerable magnitude before symptoms appear. Inhalation of irritants and dust and the presence of coarse foreign bodies are also causes. Various constitutional vices—such as chronic heart disease, tuberculosis,

syphilis, anemia, etc.—are also important causes. The extreme aridity of houses heated by modern methods undoubtedly predisposes to catarrh. The presence of tumors, particularly of polypi, is said to favor the condition, or may be an important determining cause; in other cases overgrowth of the mucous membrane may assume polypoid characteristics, a fact supporting the view that the inflammation leads to tumor formation. Inflammatory processes may be *hypertrophic* or *atrophic*, and may or may not be associated with fetid discharge (ozena). There is a form of nasal inflammation that has received the name *purulent rhinitis*, by reason of the pus-like character of the discharge; an inflammation of this kind not infrequently follows the presence of foreign bodies, nasal tumors, suppurative processes in accessory sinuses, acute infection, such as gonorrhea, and the ulcerative stages of the chronic infections, particularly glanders, tuberculosis, and syphilis.

Tuberculosis and *syphilis* are the most common chronic infectious inflammations; *glanders* usually manifests itself here, as does *rhinoscleroma; leprosy* and *actinomycosis* may occur.

The mucosa being continuous with that of the sinuses of the superior maxilla, the frontal and ethmoid bones, and by the Eustachian tube with the middle ear, inflammation once established in the nose may extend to these structures, where, by reason of faulty drainage and inaccessibility, chronic processes ensue. The sinuses lying in proximity to the brain may afford means for intracranial infection, as seen in middle-ear disease leading to cerebral abscess, and in the tubercular meningitis asserted to follow tuberculosis of the nasal cavities and their appendages.

Tumors.—*Adult Epithelium.*—*Adenomata* of the nasal mucous membrane occur more commonly as the pharynx is approached, but, on the whole, are not frequent; they are mostly cystic, owing to inclusion of a mucous gland, ordinarily by inflammatory tissue. *Papillomata* or warts occur in the vestibule. A hairy papilloma resting on a base of fat (lipomatous tissue) has been described. It is believed to be congenital (Arnold). *Carcinoma* of the nose is rarely primary, usually extending to the nasal cavity from the mouth or face; it is generally of the epitheliomatous type rather than glandular. *Fibromata, chondromata, osteomata,* and *myxomata* occur. True myxoma is rare, but *fibromyxoma* and pure fibroma are of not infrequent occurrence; *nasal polypi* are most commonly one of these two varieties. *Sarcomata* occur in the nasal cavity, arising from the fibrous tissue of the submucosa, the periosteum, or, rarely, the bone; they occasionally develop in the sinuses: *e. g.*, the antrum of Highmore.

Erectile tumors (*telangiectatic polypi*) are made up of numerous thin-walled blood-vessels embedded in a fibrous, mucoid, or adenomatous matrix containing more or less myxomatous tissue. They are infrequent.

Postnasal Adenoids.—There must be some doubt as to the advisability of regarding these enlargements as true tumors, and as the new growth is most frequently the result of an increase in preexisting lymphoid tissue, the term *postnasal adenoid hypertrophy* has been applied. The disease is one of infancy and childhood, and is most frequent in tuberculous families, commonly associated with some form of rhinitis, with defects of development in the osseous walls, causing stenosis, and with concomitant pharyngeal or postnasal catarrh. The growth is most marked on the posterior rhinopharyngeal wall. The masses are usually sessile, with uneven, granular, or lobulated surfaces.

Histologically, the new growth is composed of lymphoid tissue. So far as the growth itself is concerned, it usually atrophies and disappears at or about puberty. In the mean time, however, the mechanical interference with respiration, and the associated catarrh, induce a drain on the patient's general health, embarrass respiration, and may be accompanied by tuberculous infection; involvement of the Eustachian tube and an infective otitis media, with consequent deafness, may also occur.

Rhinoliths are calcareous masses occasionally found in the nose; they arise from the deposit of lime salts around a nucleus, usually a foreign body, or, rarely, from inspissated secretion.

Anosmia, or loss of the sense of smell, may be caused by (1) central lesions or (2) chronic catarrhal thickening, and contraction may pinch the filaments of the nerve, and thereby destroy them; a similar result may follow periosteal thickening, as seen in syphilis. When the sense is not destroyed, but perverted, the term **parosmia** is used. *Hyperesthesia of the olfactory nerves*, also called **hyperosmia**, is usually dependent upon central lesions or is a part of some neurosis. Exclusive of the abundant exudate seen in inflammations, and independent of any recognizable change in the membrane of the nasal cavity and accessory sinuses, there is, at times, a most marked serous discharge, constituting a true **rhinorrhea.** The cause of the condition is not known.

LARYNX AND TRACHEA.

Normal Structure.—The epithelial layers of the mucosa vary as to depth and variety of epithelium; the epiglottis and the true cords are covered by squamous epithelium, lines of which

extend between the epiglottis and cords. The greater area is covered by ciliated epithelium.

Malformations.—*Absence* of the larynx is rare. Occasionally, it is small and poorly developed (*hypoplastic*), a condition said to attend testicular hypoplasia and to follow castration. Abnormal largeness is at times noted. Combinations of the last-named conditions, giving rise to asymmetry, are more frequent. The ventricles may be abnormally large, or aberrant sinuses or pouches may extend into the perilaryngeal tissues, giving rise to a condition known as *emphysema of the neck*. From faulty union of the branchial arches fistulas may result. Clefts and fissures of the epiglottis occur. Defects in the laryngeal cartilages are sometimes observed, but are rare.

Hemorrhage from the larynx accompanies injury, severe inflammations, tubercle, and tumors, particularly the highly vascular papillomata and carcinomata; it rarely occurs from vascular distention and vicarious function. Hemorrhages into the submucosa, and even on the free surface, are sometimes present in scurvy, leukemia, pernicious anemia, and allied blood dyscrasias. Suffocation and strangulation are also causes. Intense hyperemia and extreme congestion may cause laryngeal hemorrhage.

Hyperemia occurs in the initial stage of inflammation, after violent exercise, inhalation of irritants, etc.

Congestion is noted in heart disease and lesions obstructing the return of blood from the larynx, as goiter and mediastinal tumors.

Inflammations.—Inflammation of the larynx is called **laryngitis**; of the trachea, **trachitis** or **tracheitis.** Catarrhal, pseudomembranous, and gangrenous inflammations occur in the order given; the last is infrequent, and the catarrhal is common.

The catarrhal inflammations may be either acute or chronic, the former depending upon exposure, inhalation of irritant gases, extension of inflammation from adjacent mucosæ, infections and infectious diseases, such as measles, influenza, etc. Follicular distention and superficial erosions occur, but are infrequent. The vascular distention of acute inflammation, with even slight edema, interferes with the function of the vocal cords, narrows the orifice, and is the anatomic basis for the so-called **spasmodic laryngitis,** which is also known as *spasmodic, false*, or *catarrhal croup.*

Chronic catarrhal laryngitis is usually a sequence of repeated attacks of acute inflammation. It is favored by continuous exposure to irritation, by the presence of constitutional vices,—such as syphilis, tuberculosis, contracting kidney, gout, etc.,—and by local disturbances of nutrition, such, for example,

as are seen in the stagnant circulation of chronic heart disease and in long-continued pulmonary inflammation, emphysema, etc. Epithelial thickening (pachydermia laryngis) of the vocal cords, submucous cellular infiltration, and even papillomatous excrescences may result. Rosenberg regards singer's nodes as a result of inflammation involving the duct of Fränkel's glands, and not true epithelial indurations (pachydermia), as believed by Virchow.

Pseudomembranous inflammation is almost exclusively dependent upon the bacillus of diphtheria, which here rarely induces the gangrenous lesions seen on the pharynx and tonsils. Hemorrhagic inflammation is less frequent. Suppurative inflammation occurs as pustules, as in smallpox, or as a purulent infiltration of the submucosa, most commonly secondary to an antecedent edema of the submucosa. Pus-formation may be diffused in the submucosa or may be circumscribed (abscess), in which case it may rupture into the larynx, infiltrate the perilaryngeal tissues, or dissect into the esophagus. If evacuation be established and drainage secured, repair may follow. Catarrhal, pseudomembranous, and gangrenous inflammations have been noticed in typhoid fever, as have the suppurative and perichondroid inflammations.

FIG. 269.—TUBERCULAR ULCER OF THE MUCOUS MEMBRANE OF THE TRACHEA. VERTICAL SECTION OF THE TRACHEAL WALL.—(*Schmaus.*) × 10 diameters.

K. Cartilage. *e*, *e*. Epithelial layer of the mucous membrane. *t*. Tubercles in the mucous membrane. (Submucosa.) *g*. Ulcer extending from *e* to *e*.

The **chronic infectious inflammations** are extremely prone to invade the larynx; syphilis and tuberculosis are the most frequent, but when leprous infection or glanders occur, the larynx rarely escapes. (For morbid anatomy, etc., see chap. VIII, part II; also chap. VII, part III.) Primary tuberculosis is rare, but does occur; tubercular ulcers usually are posterior, and begin low and ascend, in contradistinction to syphilis, which is higher and descends; cicatrization and contraction take place in syphilis,

but rarely in tuberculosis. Although rare, syphilitic and tubercular ulcers may be side by side * and differentiation of the gross lesions may be impossible. The finding of anatomic tubercles containing the bacillus affords the necessary diagnostic evidence.

FIG. 270.—PERICHONDRITIS WITH LARYNGEAL ULCERATION.—(*Specimen from patient dead of typhoid fever.*)

The area shown near the center indicates the outline of an ulcer, the floor of which was smooth and healing. Near the center is seen a black necrotic mass of exfoliating cartilage.

Perichondritis, or inflammation of the perichondrium, occurs as the result of acute inflammations of the mucosa; more commonly, however, it follows tuberculosis, syphilis, or inflammation,

* Griffin, "The Laryngoscope," No. 4, 1897.

extending from surrounding structures; typhoid fever, smallpox, and, less frequently, other acute infectious processes may cause it. Pus forms in the perichondrium, escapes through the submucosa and mucosa, and an ulcer follows in which exfoliation of the cartilage takes place; the necrosed cartilage falls into the larynx and is expectorated, or it may, acting as a foreign body, reach a bronchus, or, lodging in the air-passage at any point, may give rise to acute obstruction. After exfoliation, in nontubercular cases, the ulcer tends to heal.

Calcification of the cartilages is seen in the old, rarely in the young or middle-aged.

Edema of the glottis is in most cases an inflammation. *Acute edema* follows or accompanies (1) inflammations of the mucosa, as already described; (2) inflammations of adjacent tissue (*e. g.*, pharynx); (3) erysipelas and other infections not included in the previous list. It tends toward suppuration, and is therefore a true inflammatory process, probably an infection of the submucosa.

Chronic edema may follow or precede the acute form, or may arise independently, and this is by far the most common. It may occur as a result of venous distention, as seen in valvular heart disease, and from compression of the veins returning from the larynx by tumors, cysts, goiter, etc. Pulmonary emphysema, dropsical affections associated with kidney diseases, or obstructive heart lesions may terminate fatally through an attack of edema of the glottis; chronic infectious processes in the vicinity are not infrequently associated with a mild degree of edema. In either form edema may threaten life by occlusion of the passage—inflammatory stenosis.

Stenosis of the larynx occurs in two forms, exclusive of the malformations—(1) functional and (2) organic. *Functional stenosis* results from paralysis of the muscles that open the larynx or from spasm of those that close it. The former most commonly results from faulty innervation, due to central disease of the nerve, trunks, or brain, or from pressure on the nerves by tumors, aneurysms, etc. That paralysis may follow degeneration of the muscle without antecedent nerve change seems doubtful. *Organic stenosis* follows contraction in healing ulcers, notably the syphilitic ulcerations; laryngeal tumors, edema, and inflammations; pressure from without, as in tumors and enlargements of the surrounding glands, and aneurysm; hemorrhage into the mucosa, fracture, or other injury to the laryngeal structures, as in throttling. Laryngeal obstruction depending upon the presence of false membrane, congenital hypoplasia, and foreign bodies is

not correctly considered among the stenoses, although the influence upon respiration is practically the same.

Tumors of the Larynx.—*Adult Epithelium.*—*Papillomata* are by far the most common. They may consist of fibrous as well as epithelial increase in the papilla, and may be soft and dendritic, or they may be pachydermatous or dense from the

FIG. 271.—TRACHEAL AND PARTIAL LARYNGEAL STENOSIS FOLLOWING CICATRIZATION OF A GUMMA.

The syphilitic lesion has evidently destroyed parts of two tracheal rings, and extended upward into the larynx. The cartilage on the right shows results of a slowly progressing perichondritis, with beginning necrosis, although the overlying mucous membrane is not involved.

thickening and subsequent hardening. All forms of papilloma are likely to undergo transformation into cancer.

Embryonic Epithelium.—*Epithelioma* involving the larynx is usually of the squamous type, and may be dendritic, like papilloma. Papillomata occur in childhood and in adolescence; the cancer, in middle life or later. The cylindric-cell and tubulated

varieties of epithelioma also occur. In rare instances a papilloma may accompany or may even follow a cancer, while the development of cancer from papilloma is not uncommon.

Adult Connective Tissue.—Fibrous polypi, like those described in the nose, both hard and soft, may occur in the larynx. Like the papilloma, the location is most commonly on the vocal cords. *Myxomata* are rare in the larynx, but may occur. *Chondromata* have been observed. Embryonic connective-tissue tumors (*sarcomata*) are exceedingly rare in the larynx and trachea.

BRONCHI.

Normal Structure.—The bronchi consist of a series of tubes lined by columnar epithelium, which is ciliated down to the terminal tubes, where it becomes cuboid and nonciliated; the wall of the bronchus is composed of fibrous and elastic tissue and of a small quantity of unstriped muscle, the latter being most abundant where the cartilaginous rings fail to surround the tube completely. The mucous membrane of the larger bronchi contains numerous mucous glands.

Malformations.—When arrest of development has occurred previous to the structural completion of the lung, the bronchi may terminate as blind pouches or may be absent. Congenital narrowing or the reverse may be found. (See Bronchiectasis, p. 563.)

Hyperemia and congestion manifest themselves under the same conditions and with the same changes as have been elsewhere noted in the trachea, etc.

Hemorrhage.—(See Hemoptysis, p. 567.)

Inflammation.—Catarrhal inflammation, both acute and chronic, is one of the most frequent diseases of the bronchi. In the larger tubes the glands of the mucosa may stand out prominently, constituting a *follicular bronchitis*. When the inflammatory products are abundant, clear, serous fluids, the name *bronchorrhea* is given; *bronchoblennorrhea* is the term applied when a puriform expectoration is present. These probably represent only different stages of the inflammatory process. *Putrid* or *fetid bronchitis* is due to decomposition of the bronchial secretion by saprophytic bacteria; it is usually associated with bronchiectasis, the dilated cavities affording storage sufficient to permit the development of decomposition. Similar facilities are present in pulmonary gangrene, in empyema with perforation of a bronchus, in tubercular cavities, etc. By some it is held to be due to a specific organism; by others, to the colon bacillus. Actinomyces,

oidium albicans, and possibly other organisms may bring it about.

Chronic bronchial inflammation tends toward the development of fibrous tissue around the bronchi—the *peribronchitis chronica* of German writers; in other cases atrophic changes occur in the mucosa; bronchiectasis may follow; emphysema is an almost constant accompanying lesion. Of the *chronic infections*, tuberculosis is the most common; it may occur as a miliary process or as a caseous area around the bronchus, which, breaking down, forms a cavity which can be only with great difficulty differentiated from bronchiectasis. *Gangrenous* and *hemorrhagic inflammations*

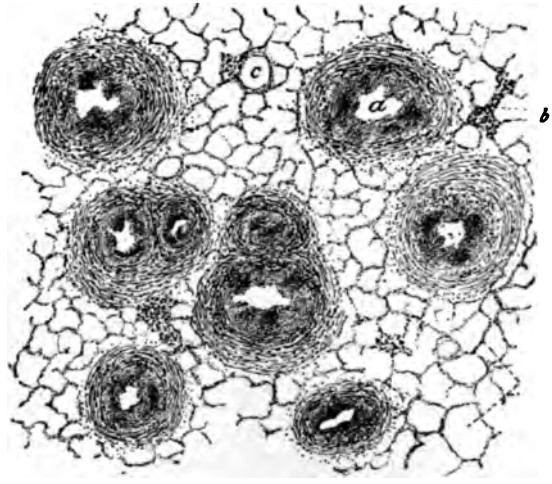


FIG. 272.—CHRONIC CASEOUS BRONCHITIS, TUBERCULOUS BRONCHITIS, CASEOUS SOFTENING OF THE BRONCHIAL WALL, WITH THICKENING OF THE PERIBRONCHIAL TISSUE, PERIBRONCHITIS CHRONICA.—(*Schmaus.*)

a. Bronchus with thickened and caseous wall surrounded by a layer of fibrinous tissue. Several other bronchi are shown, but representing slightly different degrees of the process. *b*. Transverse section of interlobular septum. *c*. Blood-vessel.

of the bronchi are rare, and follow or accompany pulmonary gangrene, the inspiration of powerful irritants, etc.

The *fibrinous* or *pseudomembranous inflammations* of the bronchi are usually chronic, although an acute form is abundantly present in laryngeal diphtheria, in fibrinous pneumonia, and, less commonly, in other acute infectious diseases. (For pathology of the acute, chronic, and infectious inflammations of mucous membranes see p. 536.)

Suppurative inflammation of the peribronchial lymphatics may follow pleurisy,—more especially the suppurative

form (empyema),—abscess, gangrene, septicemia, pyemia, and allied infectious diseases. It is not recognizable during life, and postmortem shows as a purulent infiltration of the peribronchial tissues, at times extending to the lymphatic glands; if not due to, it is usually followed by, septicemia or pyemia. (See Pulmonary Suppuration, p. 574.)

Pigmentary infiltration of the bronchial mucosa and the effects of congestion have been studied. (See Infiltrations of the Mucous Membranes, p. 533.)

Stenosis of the bronchi may be due to swelling of the mucosa (bronchial turgescence, such as occurs in bronchial asthma); to occlusion, more or less complete, by fibrinous exudate or mucus; to pressure from peribronchial exudates, as in tuberculosis, or to contraction of newly formed cicatricial tissue, as in syphilis; to intrabronchial tumors; or to pressure from neoplasms of the lung or peribronchial glands or from aortic aneurysms, mediastinal tumors, and tumors of the esophagus. Foreign bodies may obstruct or occlude the bronchi. Atelectasis and atrophic or inflammatory changes occur in the lung tissue beyond the point of stenosis, while bronchiectasis may develop in the bronchus back of the strictured point.

Bronchiectasis, or dilatation of a bronchus, occurs in two forms—(*1*) *congenital* and (*2*) *acquired.* (1) The congenital form is unilateral, usually general, affecting many or all of the bronchi of that side (*bronchiectasis universalis*, Grawitz). The condition is a tubular or cylindric dilatation of the bronchial tubes. It is very rare, and the cause is but poorly understood. (2) *Acquired bronchiectasis* arises as the result of chronic bronchial inflammation, interstitial pneumonia, atelectasis, adhesions of the pleura, tuberculosis, peribronchial inflammations, usually tubercular, or accumulated bronchial secretions. Two conditions are necessary in bronchiectasis: (1) Some lesion leading to softening of the bronchial wall; (2) a distending force. All the foregoing offer these, and any condition inducing them may bring about dilatation. The inflammatory conditions soften the walls, and the attending cough offers the distending force; where an area of the lung is collapsed, the bronchus delivering air to that part is subjected to inspiratory distention, and commonly dilates. A number of observers have described a form of bronchiectasis involving the bronchioles, and hence called **bronchiolectasis.** The condition is said to develop acutely, and hence is termed acute bronchiectasis, or bronchiolectasis.

As a rule, the bronchiectatic cavities are fairly evenly distributed within the lung. In over fifty per cent. of the cases but

one lung is involved. Any part of the lung may contain dilated bronchi, but apparently they are most frequent in the lower and middle lobes. Statements to the contrary probably arise from failure to differentiate the cavities of tuberculosis from bronchiectatic cavities.

The *bronchiectatic cavity* may be uniform, cylindric, or tubular, as in the bronchiectasis universale; fusiform, or spindle-shaped, saccular, globular, or irregular in outline; the last is found in bronchiectasis due to interstitial pneumonia. As one part of the bronchial wall is nearly always weaker than some other point, the cavity is rarely symmetric. The cavity of a dilated bronchus may be eight centimeters, or even larger, in diameter, and from that size down to almost inappreciable dilatation. The cavity may be differentiated from a tubercular cavity by the following points: In bronchiectasis the wall may be smooth and lined with epithelium, and may contain, at points, if not throughout, remnants of the normal bronchial wall; if the cavity be roughened by ulceration, it is at the most dependent point. The points of entrance and exit of the bronchus may be seen. No shreds of blood-vessels or of other bronchi or bronchioles are to be seen in the wall or extending into the cavity. Recognition of the cause may aid in differentiation. The absence of tubercle bacilli and of anatomic tubercles in the wall, of course, excludes tuberculosis.

The cavity contains accumulated secretion, and this is probably fetid, owing to saprophytic infection and decomposition. Ulceration may open the peribronchial lymphatics and infection of the pulmonary tissue may ensue, with pulmonary abscess, gangrene, etc.

Tumors of the bronchi are exceedingly rare as primary growths.

LUNGS.

Normal Structure.—The bronchi, by dichotomous division, eventually terminate in the infundibula, around which are arranged the air vesicles. The ciliated epithelial cells lining the bronchi become low, nonciliated, and eventually flat polygonal cells, which, in turn, are transformed into flat, pavement-like cells in the air vesicle. The wall of the air vesicle is composed of fibrous and elastic tissue, in which ramify the capillaries derived from the pulmonary artery. The nutrition is dependent upon the bronchial circulation.

Malformation.—Absence of a whole lung or of a part of a lung occasionally occurs; absence of both lungs has been ob-

served. Additional lobes have been found present in numerous instances. Aberrant lobes, or even a miniature lung unconnected with any normal or patulous air-passage, have been observed. Hypoplastic or underdeveloped lobules or rarely lobes have been found, and the reverse may occur. Arrest of development involving part of a lung, or it may be all of one lung, is usually associated with the corresponding overdistention of the developed portion of the lung, constituting a compensatory emphysema. (See Emphysema.)

CIRCULATORY DISTURBANCES.

Hyperemia (active congestion or active hyperemia of some writers) occurs in violent exercise, in the initial stage of acute inflammations of the lungs or pleuræ, in the chill or cold stage of malarial and septic paroxysms, and in allied conditions that incite powerful cardiac action; excessive heat or cold is also said to favor hyperemia; pulmonary hyperemia is said to precede death from disease of the coronary arteries; disease and injury of the pons or medulla are possible causes. Localized hyperemia occurs around diseased areas that interfere with the circulation, such as infarction processes, circumscribed catarrhal or croupous pneumonia, and areas invaded by any of the chronic infectious diseases to which the lung is liable.

If the lesion be purely a hyperemia, the condition to be noted in the initial stage of fibrinous pneumonia will be found.

Congestion (passive hyperemia or passive congestion of some writers) is dependent upon the slowing of the pulmonary circulation from (1) deficient force from the right heart; (2) from non-aeration of the lung; (3) from backing of blood from the left heart, as in valvular disease of the mitral orifice, associated with obstruction or regurgitation, either condition permitting of increased blood pressure within the lung. In the vast majority of cases more than one of these causes will be found acting. Two forms of pulmonary congestion are constantly observed—(1) *brown induration* and (2) *hypostatic congestion*. Brown induration has already been referred to. (See p. 535.) It results from disease of the left heart most commonly, but may be brought about when any obstacle beyond the pulmonary capillaries impedes the circulation. Pulmonary edema is most commonly associated with chronic congestion.

Hypostatic congestion arises as the result of weakened heart action, deficient respiration, and the influence of gravity. It is found in febrile conditions (*e. g.*, typhoid fever), in the aged, and

after prolonged stay in the recumbent posture, as when a fractured limb is treated with the patient prone.

This form of congestion has also been noted in morphin-poisoning and associated with, or following, disease and injuries of the brain; in the latter case the condition is further favored by deficient movement or innervation of the side affected, and will therefore manifest itself most likely when paralysis is present. All forms of coma favor the development of hypostatic congestion.

Being influenced by gravity, the dependent part of the lung shows the change; this is most commonly the posterior part. The affected area is dark in color, often almost black, much heavier than normal, pits on pressure, and when cut into, blood or bloody serum streams from the cut surface. The blood may be retained in the vessels and the serum in the intervesicular structure, in which case the affected area floats in water; not uncommonly, however, the serum, and even some blood, permeates the vesicular wall and involves the air vesicle, in which case areas may be selected that sink in water. This latter condition has been called splenization and *hypostatic pneumonia*. When hemorrhage or infiltration of blood occurs in the vesicular wall, the changes observed may resemble those seen in diffuse pulmonary apoplexy.

The anatomy, as just given, indicates the histology. In poorly marked cases, after hardening, very slight histologic changes may be evident; a few leukocytes and mucous cells in excess will be present in the vesicles; the vesicular epithelium will be found cloudy and often desquamating. In more marked cases, in addition to the foregoing, the vesicles will contain more or less blood, and infiltration of the pulmonary connective tissue by serum and blood may be demonstrable.

Pulmonary edema occurs, as already indicated, in any prolonged hyperemia or congestion, certainly in the latter. It is brought about by a slowed or impeded circulation, aided by some poorly understood alteration in the blood, and, probably, an associated degenerative change in the capillary walls. It also accompanies blood dyscrasias, such as the various forms of anemia, Bright's disease, and cancerous disease of the lung or mediastinum, and occurs as a terminal event in the death agony when the latter is, from any cause, prolonged. Why it does not always occur in congestion, and in the other conditions just given, is not apparent. Aside from the general edema, a local process, similar in kind, manifests itself around neoplasms, infarction, and inflammatory and tubercular areas in the lung, and is spoken of as *collateral, circumscribed,* or *localized edema.*

Morbid Anatomy.—The edematous lung is swollen, wet, and boggy in appearance, pits on pressure, collapses slowly, if at all, and is heavy, but does not sink in water; on section, serum flows from the cut surface, and if congestion be present, the serum is bloody.

Hemoptysis (*Spitting of Blood; Bronchopulmonary Hemorrhage*).—*Causes.*—(1) Trauma; severe falls; blows upon the chest; wounds of the lung, bronchi, etc. (2) Tuberculosis: (*a*) primary, miliary, or ulcerative lesions of the passages; (*b*) rupture of vessels, whether aneurysmal or not, in cavities. Tuberculosis is by far the most frequent cause. (3) Laryngeal, tracheal, or bronchial ulceration, arising from any cause, opening a bronchial artery. Bronchiectasis is rarely a cause. (4) Pulmonary congestion, such as accompanies valvular heart disease; hyperemia, as in the stage of engorgement of acute fibrinous pneumonia. (5) Malignant tumors of the lung or tumors involving the bronchi, trachea, or larynx; papillomata of the larynx, rarely from other simple neoplasms. (6) Hemoptysis has been observed in leprosy. (7) Necrotic processes in the lung: *e. g.*, abscess, and notably gangrene. (8) Aneurysm (*a*) of the pulmonary artery or its branches, as occurs in tubercular cavities; (*b*) of the aorta; (*c*) of the innominate artery; (*d*) of the internal carotid; (*e*) of the subclavian. (9) Vicarious hemorrhage. (10) Hemoptysis in arthritic diathesis. (11) Blood dyscrasias, as seen in purpura and scurvy. (12) Parasitic hemoptysis, or endemic hemoptysis, a disease common in China and Japan, due to an invasion of the lung with the distoma westermanni or pulmonale. (13) In a certain number of cases no assignable cause can be found; in a few of these the hemorrhage may recur a number of times without any discernible organic lesion preceding, accompanying, or following it. To this class properly belong vicarious hemoptysis, as well as that which may accompany pregnancy; in the latter instance cases are recorded in which successive pregnancies have been accompanied by recurring hemoptysis.

The effect of hemoptysis may be local or general. Locally, a slowly manifested hemorrhage may be aspirated into the air vesicles and gradually inundate the bronchial system; a marked or severe hemorrhage may rapidly inundate and be immediately fatal. The hemorrhage may develop so slowly that no phenomena during life may be observed, and postmortem much of the lung may be found filled with the effused blood. If large cavities are present in the lung, a fatal hemorrhage may fill them and cause death without any blood-spitting. The general phenomena are those of shock. The lung postmortem will be found

more or less distended or inundated with blood if death occur during the attack; antemortem and postmortem coagula will be found in cavities, when such are present, and in the bronchi. As the patient does not commonly die from the hemorrhage, the causes may be of more interest than the condition.

Hemorrhagic infiltration, or infarction (*pulmonary embolism*, or *pulmonary apoplexy*), consists in the arrest of the circulation in a given area of the lung, vascular rhexis with infiltration of the intervesicular structure, and effusion of blood into the air vesicles.

Causes.—Blocking of the pulmonary artery by a thrombus (autochthonous embolism) or an embolus. The latter usually reaches the heart from the venous circulation, as in phlegmasia alba dolens, or arises in the heart, notably the right auricle. The processes of thrombosis and the origin of emboli have been considered. (See p. 267.) Where a thrombus forms, fibrinous plugs occlude the vascular supply to the affected part, and a cone-shaped area marks the outlines of the infarct. With clearly formed areas of hemorrhage, not to be differentiated from known areas of infarction, sometimes no embolus or thrombus, or source of either of these bodies, can be demonstrated. Feebleness of the circulation favors the occurrence of pulmonary infarcts.

Morbid Anatomy.—Postmortem, the changes found depend somewhat upon the extent of the area involved and upon the age of the infarct and its character.

When the lodged embolus is massive, occluding the pulmonary artery at its bifurcation, and when death occurred immediately upon its lodgment, the lung does not show the condition here considered as pulmonary apoplexy; it may show almost no change. In typical cases of recent embolism the infarct appears, under the pleura, as a dark-red, almost black, spot, varying in diameter from one centimeter to five centimeters, rarely larger, and on section is found to be wedge shaped, truly conic, with the apex of the cone directed toward the center of the lung. The color will vary from a gray, in extremely leukemic blood, to a black; as the process grows older the color passes from black to reddish-brown, and, with the gradual resorption of blood coloring-matter and resolution, the normal color may be, in favorable cases, resumed. While the typical pulmonary infarct is conic or wedge shaped on section, the extensive anastomosis of the pulmonary circulation often affords so abundant a collateral blood supply that the area may be almost globular, pear-shaped, and ovoid on section. The pleura over the area is at first normal, but soon shows a beginning exudate. There is usually considerable edema surrounding the infarct. If the

process is not infected—it is the noninfected variety which is now under consideration—and the area is small, it is possible that absorption may occur. It is probable, however, that a certain amount of cicatricial tissue always develops, and, in not a few instances, a fibroid area remains.

Histologically, the area consists of plugged vessels, with blood infiltrated into the septa and vesicles. In a short time after the infiltration the blood coloring-matter is yielded up by the red corpuscles, which also break down. The leukocytes increase in number, and, if the area involved be small, the products may pass off by the lymphatics, which, in many cases, become permanently pigmented by the process. If the area be larger, the tissue reaction greater, some fibrous tissue results; in more marked cases a puckered, pigmented, fibrous area forever marks the site of the lesion. If the bronchial artery, as well as the branches of the pulmonary artery, be occluded, the area may undergo a simple softening, fibroid change may occur around it, and lime salts may infiltrate it. The embolus causing the process may organize *in situ* and permanently occlude the vessels, or resolution may occur.

If the embolus contained bacteria, or should the area of the infarct become infected by the cocci of suppuration, an abscess results; if the saprophytic bacteria gain ingress and survive, gangrene may be engendered; if the embolus represented a part of a malignant tumor, a new focus of development is assured. Emboli containing the specific infectious agent of the chronic infections engender those processes in the lung. The emboli associated with the latter processes—abscess, gangrene, neoplastic growth, and chronic infections—are so small that little hemorrhagic infiltration may accompany them.

Pulmonary atelectasis occurs in two forms—the congenital and the acquired.

1. **Congenital atelectasis,** or **apneumatosis,** is that condition of the lung resulting from failure to expand following birth, the organ retaining its fetal characteristics.

Causes.—Feebleness; extremely feeble infants may not be able to expand the whole lung; plugging of a bronchus by aspirated solids, or even fluids, during delivery; imperforate bronchi associated with the collapse will usually show dilatation in the affected area, the extent of the dilatation depending upon the duration and force exerted.

Morbid Anatomy.—The condition may involve a part or the whole of one lung, or may be scattered as irregular masses in both lungs. The areas of atelectasis are usually most abundant

and largest posteriorly in the lower lobes. When the collapse has been due to inefficient respiratory efforts, a blowpipe inserted into the bronchus will usually lead to expansion. When the atelectasis is due to mechanical obstruction by foreign bodies, the collapsed areas can not be fully expanded in the manner just given. The areas are darker in color than the surrounding expanded portion, do not crepitate, and sink in water. When the areas are small and not abundant, the infant may recover; under such circumstances gradual distention may be brought about, or degenerative or proliferative changes may lead to connective-tissue substitution, followed by contraction, and, in time, but little evidence of the lesion may remain.

2. **Acquired atelectasis, or collapse,** is the condition observed when a part of the lung which has once expanded loses its air and does not refill.

Causes.—Gas, fluids, or solids occupying the pleura, the first arising from puncture of the lung or chest-wall, or both; the second from pleuritic effusions, dropsical or inflammatory, or hemorrhage into the pleura; the third from tumors. Bronchial obstruction is a most common cause; the obstruction may be a foreign body, a plug of mucus, pressure from without, as in enlarged peribronchial glands, tumors, or aneurysms. The influence of pressure may be shown in aortic aneurysm, pericardial distention, mediastinal tumors, spinal curvature, etc.; the pressure may be insufficient and the atelectasis partial at first, but if the cause continues to act, the collapse becomes complete.

Morbid Anatomy.—When the collapse affects the whole lung, as in pleurisy with effusion, the organ is squeezed up against the spine, is pink or pale gray in color, is firm and airless, is tough, tearing with difficulty, and often can not be distended; firm adhesions may bind it down, and the pleura may have become so thickened, fibroid, and resisting that reexpansion can never occur. When small areas of collapse occur, as in bronchopneumonia, in the recent state, they present themselves as small depressed spots immediately under the pleura, bluish-purple or bluish-brown in color; occasionally lividity develops on exposure to the air; surrounding these areas the vesicles are distended (compensatory emphysema) and are pink or reddish-white, in contrast to the darker collapsed portions. If the collapse be recent and the occluded bronchus not too firmly obstructed, a blowpipe, or even firm pressure on the surrounding areas, may refill the points of collapse. Later, from stasis in the vesicular wall, the color becomes much darker, and blood escapes into the connective tissue; the mass is soft and resembles the spleen in texture **(splenization).**

Later, the blood is absorbed to a certain extent, the vesicular walls coalesce, proliferated connective-tissue cells and leukocytes form new fibrous tissue, and the mass is now in the condition known as **carnification.** With the completion of contraction and organization a firm fibroid area results, known as the **cirrhosis of collapse**; these areas contain a relative excess of pigment, are pink at first, later gray, and are said to show **gray induration.**

Emphysema.—(A) **Interstitial emphysema,** also called **interlobular emphysema,** is a condition in the lung comparable to subcutaneous or surgical emphysema, as seen by the surgeon in the subcutaneous tissues in fracture of the nose, or to the gas generated in the tissues in some forms of gangrene.

Causes.—(1) Ruptured air vesicles, as occasionally occurs in violent coughing, as in whooping-cough or in vesicular emphysema; (2) wounds of the lung, resulting from fractured ribs and penetrating wounds of the chest. In the latter condition interstitial emphysema may occur without pneumothorax, provided air does not gain ingress through the thoracic wall. It has recently been shown that pneumothorax may result from infection of the pleura by the bacillus aerogenes capsulatus of Welch. It is probable that in a similar manner an interstitial pulmonary emphysema might be induced.

Morbid Anatomy. — Interstitial emphysema may be readily detected postmortem by the large blebs found immediately under the pleura, differing from overdistended air vesicles in that the former can be pushed around from place to place beneath the pleura. When the rupture occurs near the root of the lung, not only does the air reach the surface of the organ by the interlobular connective tissue, but it may find access to the connective tissue of the neck.

(B) **Vesicular emphysema** is a condition in which the alveoli and infundibular passages are dilated.

When the emphysema consists of overdistended vesicles in one area to occupy the space and to receive the air intended for another area, the condition is spoken of as **local, vicarious,** or **compensatory emphysema.** As the condition may be acute,—*e. g.*, around an atelectatic area,— the withdrawal of the cause may terminate the emphysema; when the cause persists, the acute dilatation becomes permanent; at first there may be no wasting, but eventually the intervesicular septa atrophy and this form passes into true emphysema.

Substantive, substantial, idiopathic, hypertrophic, or **large-lunged emphysema** is a well-marked condition, readily

recognized clinically, and possessing pathologic lesions eminently its own.

Causes.—There seems to be necessary a hereditary tendency, a congenital deficiency in the lung tissue, before this disease is likely to establish itself; exactly what this hereditary deficiency is has not been determined; the view that it is a defect in the elastic tissue is entirely consistent with the facts, but probably is not demonstrable. The disease is, in this sense, hereditary, it being one of the "soil" conditions transmitted from the parent. Given the first element,—congenital weakness of the vesicular wall,—the second is heightened intravesicular tension. This may be brought about in two ways—(1) *inspiratory* and (2) *expiratory*.

1. *Inspiratory Distention.*—The vesicular distention of compensatory emphysema is, of course, inspiratory; and as true vesicular emphysema is almost always associated with catarrhal lesions, which favor atelectasis, the possibility of inspiratory distention acting as the cause must not be forgotten. The constant association of catarrhal inflammatory lesions and the plugging of bronchioles, attended by collapse in the lobules supplied, leads to compensatory dilatation of adjacent vesicles, and therefore to their overdistention; the plug of mucus now shifts, and another series of vesicles become overdistended. These processes, frequently repeated, so overdistend the elastic tissue of the vesicular wall that the normal retractile power is lost or modified, and the air vesicles are thereby rendered incompetent fully to empty themselves. The foregoing views with regard to the inspiratory hypothesis have been largely supplanted by the theory to be next discussed.

2. *Expiratory distention* acts by increased pressure applied to the lung by the bony walls, and resistance to free exit from the lung by narrowing of the laryngeal chink, glottis, epiglottidean lumen, etc.

The costal cartilages and sternum are pushed forward, the extreme normal obliquity of the ribs is altered, and the pulmonary space at the apex is increased, thus permitting distention of the lung at the apex or upper lobes and the anterior margins, these points showing the most marked change.

The causes active in increasing the expiratory effort are: (1) coughs, as in chronic bronchitis, the violent cough of pertussis, etc. (2) Increased pulmonary tension, as induced by playing wind-instruments, heavy lifting, etc.

Morbid Anatomy.—The chest is barrel-shaped; the cartilages are calcific and rigid; when the sternum is raised, the lung does

not show the normal tendency to collapse—indeed, it may not retract at all; its anterior margins extend over the pericardium to a varying degree; when removed, it does not collapse; the pleura over the affected area is pale, anemic, dry, and the unaffected areas are congested; white patches occur on the pleura —the *pulmonary albinism* of Virchow; the emphysematous lines may follow the intercostal spaces, but the disease is most marked along the anterior margins, at the apex, and, less commonly, around the margin at the base; large bullæ may be seen under the pleura, varying in size up to 0.5 or 1 cm., and at the free margin they may attain the size of 2 cm. or more. The lung fails to crepitate where the emphysema is most marked. The absence of elasticity is indicated by the fact that pits are obtained

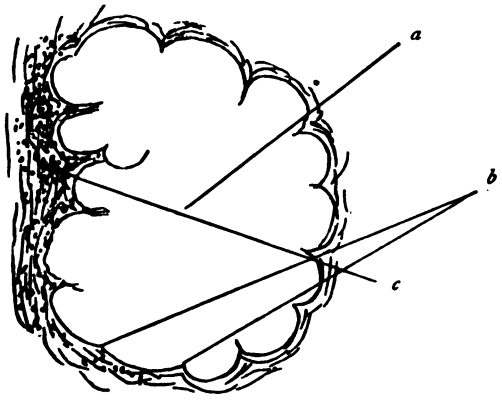


FIG. 273.—PULMONARY EMPHYSEMA.—(*Flütterer.*)
a. Emphysematous enlargement of the infundibulum. *b*. Atrophied intervesicular septa, improperly called absorbed alveolar walls. *c*. Pigment in the fibrous septum.

almost as in edema, although edema is usually absent. The color depends upon the amount of pigment. Usually, the organs are pale and the pigment is conspicuous. As a rule, the lung contains less blood than normal; and even when death has been delayed, marked congestion and conspicuous edema are frequently absent. The lung, when handled, feels like a pillow stuffed with down (Laennec). The smaller bronchi may be dilated; more or less bronchitis and peribronchial induration are always present. The longitudinal bands of elastic tissue may be traceable in the bronchial wall.

Morbid Histology.—If the lung be blown up and dried, the enormous size of the distended vesicles may be apparent; even

on section in the recent state, the atrophic remains of the vesicular walls may be discernible with a hand lens; hardened and examined, the elastic tissue will be found diminished, the vesicular septa atrophied, permitting coalescence of adjoining cells; in the process of atrophy the capillaries disappear, and this, with the loss in septa, diminishes the aerating capacity of the lung.

Changes in Other Organs.—The increased work demanded of the right heart in emphysema leads to hypertrophy and dilatation, the former in rare cases affecting the entire heart; atheroma of the pulmonary artery with or without dilatation may occur. Other organs liable to the alterations of structure incident to venous distention usually manifest that change.

(C) Atrophic or senile emphysema (*senile atrophy of the lung, small-lunged emphysema* of Jenner) is, as its name indicates, a disease of advanced life, and is essentially an atrophic lesion of a lung in which very little, if any, distending force has been exerted. The chest is small, the ribs are oblique, thus decreasing the diameters and diminishing the capacity of the chest; the respiratory muscles are atrophied and the lung is smaller than normal; the changes in the vesicles and septa already noted in substantive emphysema occur. The enlargement in the size of the vesicles is held to be due to atrophy of the intervesicular walls. The bronchi frequently show some dilatation; large bullæ are usually absent; the lung commonly collapses on opening the chest, and, in contrast with large-lunged emphysema, not infrequently shows areas of congestion, edema, and infarction. There may be some doubt as to the propriety of classifying this condition with emphysema. The fact that custom has established the precedent does not, of course, prove its correctness. A better knowledge of atrophy as it occurs in the lung would probably lead to the recognition in this form of emphysema of some atrophic manifestation analogous to that seen in other tissues in advanced life.

Acute vesicular emphysema is said to be present in acute bronchitis and after death from asphyxia; there is also reason to believe that vesicular distention is present during life in these cases. That the condition is unassociated with atrophy of the vesicular walls is admitted. In the absence of such atrophy it consists largely of functional overdistention, and is not a disease of the air vesicles.

Pulmonary Suppuration.—This condition is commonly described under the head of purulent pneumonia, suppuration pneumonia, etc., names indicating that it is some special type of

pulmonary disease rather than the usual form of suppurative lesion.

Etiologically and pathologically, and to a certain extent clinically, suppurative processes occurring in the lung possess no important difference from suppurations arising from pyogenic infection in other organs.

Primary pulmonary suppuration is an exceedingly rare condition; pyogenic infection may be brought to the lung in one of four ways: (*A*) *By the air-passages;* (*B*) *from contiguous structures;* (*C*) *by the blood;* (*D*) *by the lymphatics.*

(*A*) *By the Air-passages* (*Bronchogenic Suppuration*).—Although we are constantly inhaling large numbers of bacteria, many of them undoubtedly pyogenic, and in other ways pathogenic, the bactericidal action of the extruded epithelium, leukocytes, mucus, serum, etc., prevents ingress or pathogenic activity except the tissues be weakened by (1) *general debility*, (2) *previous local disease*, or (3) *accompanying injury.* As examples of these may be mentioned: of the first, the probability that fibrinous pneumonia in drunkards will present a mixed infection; of the second, pyogenic infection of tubercular areas, or pyogenic infection of the areas involved in lobar or lobular pneumonia, or the pyogenic infection in pneumoconiosis. In lobar pneumonia abscess formation is rare; the so-called purulent infiltration is not really pus, as it not uncommonly contains no pneumococci, and rarely, if ever, contains the bacteria of suppuration. If abscess formation takes place in pneumonia, it usually begins as scattered foci of infection, and, as such, is found postmortem; rarely, however, these foci extend and run together, the infection lessening or obliterating the circulation in the area, and more or less of a lobe may be converted into an abscess. Abscess formation in acute lobular pneumonia is still rarer.

Suppuration from injury with infection may occur as any suppuration following an infected wound. Exploratory puncture of the pleura has caused pulmonary abscess. But the form of infection with injury which brings infection with the injury, and both through the air-passages, is typified in the so-called aspiration pneumonia. Foreign bodies in the air-passages; suppurative processes in or around the larynx, trachea, or larger bronchi; deglutition pneumonia, in which, from altered innervation, food particles gain ingress to the air-passages; and allied processes, all may give rise to abscess formation by depositing an irritant, no matter how small, and with it the bacteria of suppuration.

(*B*) *Pulmonary suppuration* arising through extension of the infection *from contiguous structures* is not common, in the sense

that the abscess extends by necrosis of the lung tissue; but in the lymphatics such extension may occur. Localized or circumscribed empyema, or pleural abscess, particularly when situated between the lobes or at the base, between the diaphragm and lung, may penetrate the pulmonary tissue by a gradually extending necrosis, and eventually may find evacuation through a bronchus. Abscess of the liver or suppurating echinococcus may perforate the diaphragm and infect the lung; mediastinal abscess and other forms of peripulmonic suppuration may likewise induce pulmonary abscess. Cancer of the esophagus may lead to direct infection of the lung tissue or to infection of the air-passages.

(*C*) *Pulmonary suppuration from infection through the blood* (*hematogenic infection*) was the common sequence of preantiseptic surgery and obstetrics. Emboli containing the cocci of suppuration lodge in the lung and give rise to centers of infection, followed by abscess formation. These abscesses are small, usually multiple, superficially located, not uncommonly cone-shaped, with the base of the cone toward the pleura, into which they not infrequently rupture, giving rise to suppurative pleurisy (empyema or pyothorax), or, if communication has been established between the abscess cavity and a bronchus, thereby admitting air to the pleural cavity, there quickly results a pyopneumothorax. (See Metastatic Abscesses, p. 278.)

(*D*) *Infection of the Pulmonary Structure through the Lymph-channels* (*Lymphogenic Infection*).—An interstitial, peribronchial, or interlobular suppurative process may result from invasion of the lung tissue by way of the peribronchial lymphatics. Thus, in suppurative inflammation of the pleura the lymphatics passing through the lung structure may become clogged with infective material, or material eminently adapted to infection, and cocci accompanying this or gaining ingress to it may give rise to suppuration, which, being in the lymphatics around the bronchi, is spoken of as **peribronchial suppurative lymphangitis.** The condition can not be diagnosticated during life, and is recognized only postmortem. Pyogenic agents reaching the lung or its lymphatic system from the mediastinum or elsewhere may give rise to the process.

Morbid Anatomy of Pulmonary Abscess.—When solitary, the abscess may attain the size of a lobe; when multiple, the abscesses are usually small. The contents, in addition to pus, will be made up of epithelial debris and remnants of lung tissue, the finding of which in the sputum is a valuable aid to diagnosis. If evacuation has occurred during life, the walls may be gangre-

nous and the cavity exceedingly fetid; if the mass be small and the patient in good condition, a fibroid protecting wall may form; ordinarily, however, the wall is made up, from within outward, of a layer of (1) necrotic breaking-down lung and inflammatory tissue; (2) a layer of solidified lung infiltrated with leukocytes and young connective-tissue cells, and commonly showing hemorrhages into the alveoli and interstitial tissue; (3) edematous lung tissue. If the pleura has not been opened, the abscess wall formed by that structure will show an abundant exudate of fibrin, and some cloudy serum, varying in quantity, will probably occupy the cavity; purulent pleurisy (empyema) may occur without rupture of the abscess, but invariably occurs if rupture takes place, and is usually accompanied by pneumothorax, the latter depending upon whether the abscess communicates with an open bronchus. Rarely, a pulmonary abscess may encapsulate, as previously indicated; in lobar pneumonia, when the evacuation is complete, cicatrization has been known to occur; the same thing has taken place in hepatic abscess discharging through the lung. The majority of cases terminate fatally. Sometimes infection is wide-spread and is not associated with distinct abscess formation. Under such circumstances the condition is one of peribronchial suppurative lymphangitis, such as previously mentioned.

Attempts have been made to classify pulmonary abscesses from the cause, as, pyogenic, tubercular, actinomycotic, pneumonic, etc., but these are essentially mixed infections in the vast majority of cases, and the primary infection does not materially alter the true character of the developed malady.

Gangrene of the lung consists of two factors: (1) Death of a part of the pulmonary tissue (necrosis) or a material lessening of its blood supply and (2) infection, which must be, in all probability, a mixed infection. Infection alone does not induce gangrene; obliteration of the blood supply does not insure gangrene; the two must be present. If pyogenic infection occur in a lung whose blood supply is abundant, suppuration is induced, pus being a product of vital reaction to pyogenic mycotic invasion; if, however, the tissue be dead, if vital processes be materially weakened, the tissue resistance reduced, the nutrition greatly modified by existing lesions, or, it may be, arrested, infection gives rise to gangrene.

The causes of pulmonary gangrene, then, embrace all those conditions that materially lessen or arrest nutrition and permit infection—lobar pneumonia, aspiration pneumonia, foreign bodies in the bronchi, pulmonary embolism, bronchiectasis, suppurative

conditions in the lung, pressure, as from tumors and aneurysms on the bronchi and blood-vessels, etc. The cases of pulmonary gangrene that accompany, or, more commonly, follow, severe febrile processes are probably infections in areas of hypostatic or hemorrhagic pneumonia. Brain abscess and middle-ear and mastoid disease, by infectious thrombosis of the sinuses, may induce pulmonary embolism, which, being infected, will be likely to be followed by gangrene or abscess. The same is true of infectious processes in the venous system elsewhere.

Morbid Anatomy.—Two forms are recognized: *the diffuse or disseminated form* and the *circumscribed form.* The division made, independent of any surgical view, seems aptly adapted to the modern surgical divisions of gangrene, circumscribed and spreading. The diffuse, like spreading gangrene, is rare, and follows most commonly pneumonia, and, rarely, obstruction of the pulmonary artery.

There is not a sharp line of demarcation between the healthy and diseased tissue; a whole lobe, or the greater part of a lobe, is involved, the process being well marked at the center of the diseased area, but gradually fading into the surrounding zone of highly inflamed pulmonary tissue. In the circumscribed form there is a sharp line of demarcation between the dead and the inflamed tissue, and, although the foci may be multiple, each focus is distinct from the living pulmonary tissue.

The gangrenous mass in either case is, as a rule, extremely fetid, and during life this foul penetrating odor is imparted to the breath, and persists for hours in the sputum. The latter, when left in a conic glass, separates into three layers: the uppermost is thick, frothy, yellow or green or greenish-yellow in color; the middle layer is a clear serous fluid, but slightly tinted; the sediment is greenish-brown, occasionally pus-like, and contains the characteristic odor in its fullest concentration. Elastic fibers are not always present, although they usually are to be found. The color of the diseased tissue is dependent upon the stage and, probably to a large extent, upon the character of the infection. Early, it is brown or reddish-brown; and later, quite black. The color-changes are in part brought about by the presence of blood pigment, to which the brownish hue is to be attributed. The blackening is partly due to changes in the hemal iron as well as to the presence of iron-free pigment. The occasional greenish hue, which may be marked, may be due to changes in normal pigments or to the presence of the bacillus pyocyaneus. In the earlier stages the gangrenous tissue may retain its structure, but disintegration rapidly ensues, and a cavity with ragged irregular

walls forms, inclosing a green or reddish-yellow mass of softened necrotic tissue. Passing into, often across, the cavity are remains of blood-vessels and bronchi. By reason of the infectious character of the lesion, the blood-vessels are not occluded, as normally, by an organizing thrombus; the thrombus forming in the lumen being infected, is easily displaced, permitting of hemorrhage, which may be recurrent, and in rare cases fatal. Around the gangrenous area there is a zone of deeply congested or intensely hyperemic tissue, which is usually solidified, and outside of this an area of marked edema with leukocytic infiltration. Cicatrization and recovery may occur; the disease is more commonly fatal.

PNEUMONIA.

The term pneumonia is used to embrace all the inflammatory lesions of the pulmonary tissue, often including some of the processes already considered; for example, pulmonary suppuration is sometimes spoken of as *septic pneumonia* or *suppuration pneumonia*. When the term pneumonia is used alone, without any qualifying statement, croupous pneumonia is usually meant. The forms of pneumonia commonly considered under this heading are *lobar* or *croupous pneumonia*, *catarrhal pneumonia*, or *bronchopneumonia*, *interstitial* or *fibroid pneumonia*, and, by some writers, the desquamative pneumonia of tuberculosis.

Lobar, Croupous, or Fibrinous Pneumonia (*Pneumonitis; Lung Fever*).—The fact that the pleura is usually involved has led to the name *pleuropneumonia*. This disease is an acute inflammatory affection of the lung due to infection.

Causes.—That pneumonia is a disease due to bacterial invasion is now universally admitted. That it is, however, the result of a single organism seems no longer probable, although not absolutely disproved. The organism most frequently present is the diplococcus pneumoniæ, which was described by Sternberg as the micrococcus of rabbit septicemia, and named by him the micrococcus of Pasteur. This organism was later studied by a number of observers, and was found by Fränkel and Talamon in the lung in croupous pneumonia. (For description see p. 168.)

In 1882 Friedländer described an organism associated with pneumonia, to which he gave the name pneumococcus. As a result of later studies the organism is now held to be a bacillus. (For description see p. 177.) Croupous pneumonia, clinically and anatomically not to be differentiated from croupous pneumonia produced by the pneumococcus of Fränkel, may result from infection by streptococci, and possibly staphylococci,

although it is usually held that the presence of the latter organism is to be attributed to a mixed or secondary infection, and that, even when found alone, the primary pneumonia was due to the pneumococcus or other organism which has disappeared. The bacillus typhosus, bacillus of influenza, colon bacillus, plague bacillus, and possibly a number of microorganisms may bring about that form of solidification usually regarded anatomically characteristic of croupous pneumonia. The anatomic distribution of the lesion would indicate that infection usually takes place through the bronchi. Atypical distribution, and occasionally associated lesions, would lead us to admit the possibility of hematogenous infection.

Certain *predisposing causes* are recognized. These act in one of two ways: (1) By altering the saliva, and thereby the culture medium in which the organism is growing, and these changes in the pabulum increase the virulence of the micrococcus; (2) the predisposing elements so weaken the tissues as to permit of ready infection. The latter is illustrated by the frequency with which pneumonia occurs in drunkards, in the debilitated, in Bright's disease, after contusions of the chest, etc. The latter view seems the more reasonable, and but little importance is to be attached to the first given.

All ages are liable, but pneumonia is most frequent in three periods—early childhood, between twenty and forty, and after sixty. It is more common among males than females; where both are subject to the same influences, there is little difference. Conditions disturbing the equilibrium of the pulmonary circulation, as chronic heart disease; retention of excrementitious matters, as in uremia—in other words, any process reducing the vital powers and enabling infection to occur favors the development of pneumonia. Unhygienic environment acts in two ways—(*a*) by reducing resistance and (*b*) by favoring the accumulation of infectious material in the surroundings. The specific cause elucidates the occasional occurrence of epidemics in crowded or unhygienic quarters. There seems to be an individual susceptibility, as manifested by the frequent recurrence of pneumonia in the same individual, twenty-eight attacks having been observed in one patient (Loomis). That relapses do not occur seems to indicate a condition of acquired immunity; that such is of brief duration is also presumable from the liability to recurrent attacks. Experimentally, it has been shown, in animals, that an induced immunity may be secured by the injection of filtered bouillon cultures of the pneumococcus or a glycerin extract prepared from the growing organism. The immunity is

temporary, lasting but a few months, but during that time is transmitted, in gestation and by nursing, to the offspring. The serum of such animals has been used with apparent success in the treatment of pneumonia.

Morbid Anatomy.—Pneumonia involves, as a rule, either a whole lobe or a whole lung, most commonly the lower right lobe; the lower left lobe is next in order; third in point of frequency is double pneumonia, while pure croupous pneumonia of the apices is rare. The right apex is more frequently involved than the left. The pneumonia is double in from twelve to fifteen per cent. of the cases. The whole lobe or lung is usually in the same stage, although wandering, creeping, or migratory pneumonia, involving one lobe after another, will show different stages in different lobes; the lower lobe is most frequently involved first. In rare instances one lobe and part of another may be involved, and in different stages. Occasionally, central changes precede peripheral lesions, and the center of the lung may be gray while the periphery is less advanced —central pneumonia; rarely, the reverse may be demonstrated. In double pneumonia one lung may be further advanced than the opposite organ. In infancy and in old age the apex is more frequently the initial point of invasion; in the aged death occurs earlier in the attack than in the adult. When the disease is one-sided, the unaffected lung is commonly deeply hyperemic and congested.

Three stages are recognized: (1) Engorgement, (2) red hepatization, and (3) gray hepatization.

State of Engorgement.—When the chest is opened, the organ does not retract or collapse with its wonted rapidity; there may be a slight shrinking in volume, but the general contour of the organ is likely to be retained. The lung, or the area involved, is red, often a scarlet hue. Crepitation is present throughout, but is less distinct than normal; the specific gravity is greater than in health, as is shown by the fact that while the lung floats, it does not float so "high" as the normal organ. Occasionally, the pleura shows evidence of beginning inflammation. (See p. 476.) On section, the color is uniform; as a rule, blood oozes from the cut surface, and while in the majority of the cases the blood is thick, flowing slowly, in some cases an abundant transudate of serum appears immediately on section, which, mixing with the blood, bathes the incised surface, and drips, or even runs, from the dependent edge.

Histology of this Stage.—On microscopic examination the capillaries of the vesicular walls are found enormously distended, tortuous, and even saccular; the epithelium of the vesicles

is swollen and, in places, desquamating; in the few vesicles with marked desquamation some leukocytes and red blood-corpuscles may be demonstrated. The subpleural and interlobular connective tissue shows also the engorgement, and the lobules may be outlined under the pleura by the intensely engorged vessels.

This stage lasts from a few hours to two or three days; rarely the latter. It seems reasonable to suppose that in the last moments of life, or even after death has apparently occurred, solidification may develop, or, having already developed, may extend. Thus, the author has made postmortems after the most experienced clinicians had, but a few moments before death, outlined the area that seemed solid; in not a few of these cases has the solidification been found far beyond the outlines indicated by the physical examination made just before death. This offers some consolation for undiagnosticated areas of solidification, but it is also explained by assuming that, after death, the lung rises, as a result of retraction or partial atelectasis of the unsolidified areas above. Death rarely occurs in this stage except when great exposure, an alcoholic debauch, or other previously debilitating conditions are incident to the attack.

The stage of engorgement is often found in one part of the lung when another area is more advanced, or in one lung when its fellow is solidified. It seems reasonable to assume that, in very rare cases, recovery may occur without further progress of the morbid process.

Stage of Red Hepatization.—The stage of engorgement terminates by the distended blood-vessels pouring out the inflammatory exudate into the air vesicles, and thus, by excluding the air, bringing about the stage of solidification. The lung, or affected area, on opening the chest, shows absolutely no tendency to retract; it is voluminous, and may be marked by the ribs; the color is darker than the first stage, or rather more of a brown or reddish-brown; the area involved is solid, and the absence of air is shown in the entire freedom from crepitation, in the absolute dullness, great weight, and, when thrown into water, the rapidity with which the part involved sinks. On section, the organ is dry, rough, and granular; a finger passed over the scraped surface gives to the observer the impression of a rough surface, not unlike ground glass; this and the granular appearance are due to the plugs of fibrin that occlude the vesicles and on section project; they may be scraped out or picked out with a needle, and often an infundibulum with attached cast of the vesicles, or a bronchial plug, may be removed. The area is friable, and gives way when the finger is thrust into it; a slice cut from the

Lung, Croupous Pneumonia. Stage of red hepatization.
(*Fox's Atlas.*)

surface may break when bent; there is nothing more characteristic than this fact. The weight of the normal lung may be 600 grams; the lung in croupous pneumonia may weigh three or four times as much. (See Plate II.)

Morbid Histology.—On microscopic examination the blood-vessels are less distended than in the preceding stage, although they are still fuller than normal. The inflammatory exudate poured out from the vessels now occupies the vesicular cavity. When the exudate passed from the vessel it was liquid (liquor sanguinis), but in the vesicle coagulation of the fibrin has solidi-

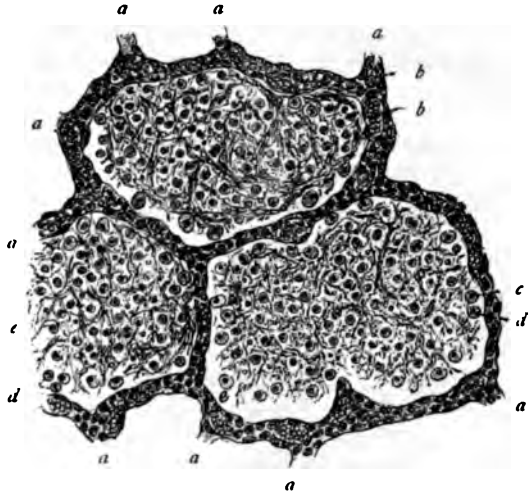


FIG. 274.—THREE ALVEOLI FILLED WITH FIBRINOUS EXUDATE. CROUPOUS PNEUMONIA, STAGE OF HEPATIZATION.—(*Schmaus*.) × 250 diameters.

a, *a*, *a*, *a*, *a*, *a*, *a*, *a*, *a*. Alveolar septa with somewhat distended capillaries, as at *b*, *b*. *c*. Meshwork of fibrin occupying the cavity of the air vesicle. Two other air vesicles, also filled, are shown. In this solidified exudate are entangled desquamated epithelial cells, *c*, from the alveolar wall and leukocytes, *d*, *d*.

fied the intravesicular contents and entangled the cellular elements present. With the transudation of the liquor sanguinis leukocytes (by diapedesis) and erythrocytes (by rhexis) escape into the vesicular cavity. Thus there are found in the vesicle leukocytes, red corpuscles, and a few desquamated epithelial cells entangled in a meshwork of fibrin fibrillæ. This fibrin may run as a net from point to point or may traverse the vesicle in straight lines; the fibrin lines may be parallel. The number of leukocytes present in the vesicular cavity increases as the process advances. The small amount of epithelium contrasts strongly

with the abundance of that element in the air vesicles in bronchopneumonia. The demonstration of the presence of fibrin is best accomplished by Weigert's method. (See p. 251.)

The solid exudate extends into the bronchiole, and may, in rare instances, reach bronchi of considerable size. The connective tissue of the lung also shows some change. The vesicular

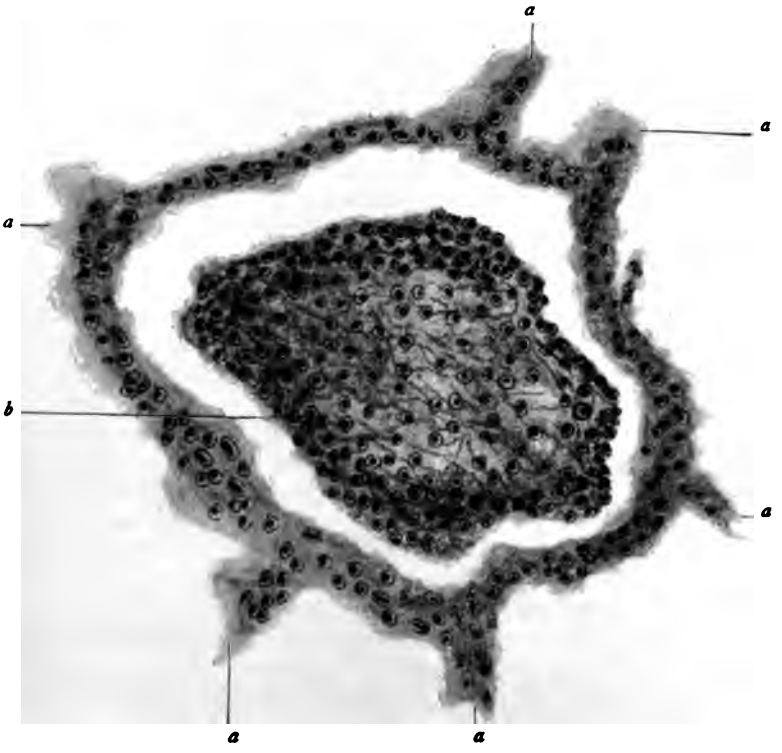
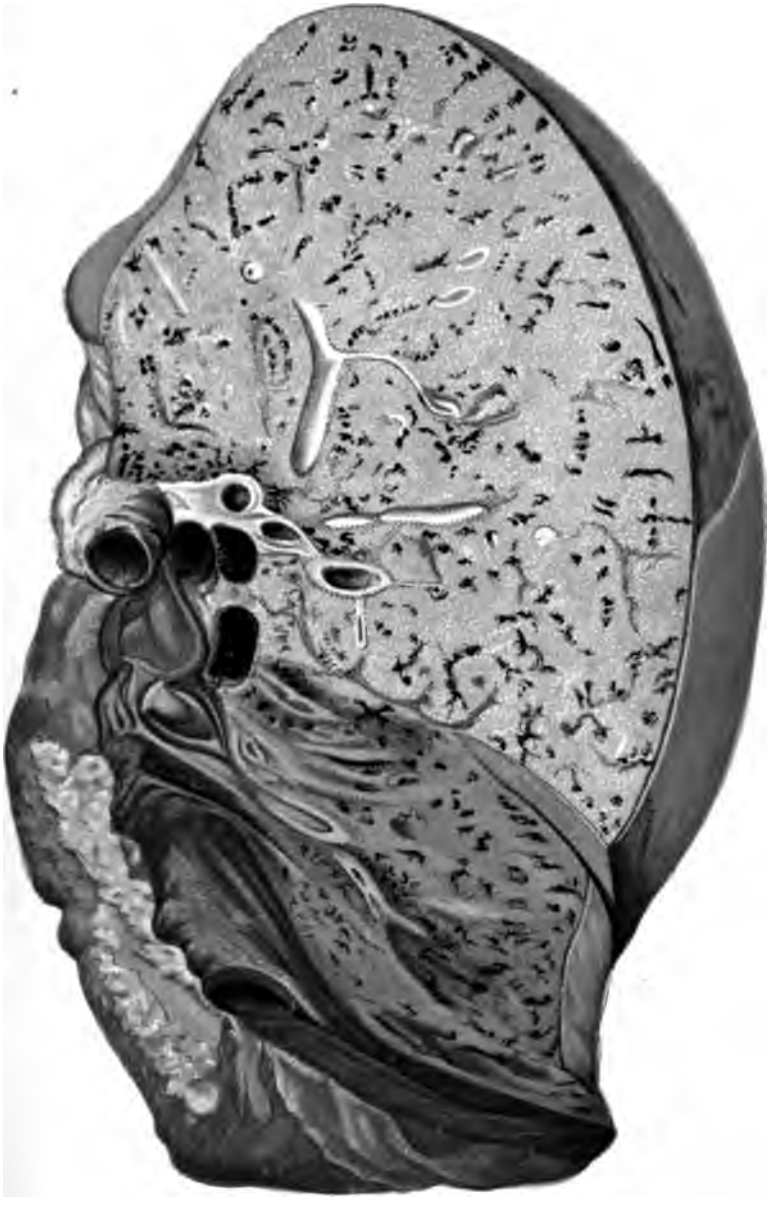


FIG. 275.—CROUPOUS PNEUMONIA. SINGLE AIR VESICLE IN THE SECOND STAGE, WITH SLIGHTLY CONTRACTED EXUDATE. (⅙-inch objective, 1-inch ocular.) Much higher magnification than in figure 276, with the object of bringing out the fibrinous network.

Specimen fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a, a, a, a, a, a.* Vesicular walls. *b.* Exudate in the air vesicle; during life the unoccupied area around the exudate either contained serum or the contraction may have occurred during fixation and hardening.

wall contains a number of leukocytes, but they are less abundant than in catarrhal pneumonia. The bronchial wall is also infiltrated. Suitably prepared sections usually show abundant pneumococci, with the occasional presence of other organisms, to which reference has been made.

PLATE III.



Lung, Croupous Pneumonia. Stage of gray hepatization. The pleura on the right and at the base shows the fibrinous exudate, modified from Bollinger.

If evidence of pleurisy did not develop in the earlier stages, it is certain to do so now. A thin plastic layer or a marked fibrinous exudate may be present. When a past pleurisy has obliterated the sac by universal adhesions, the exudate may be poured out into the adhesions, when these are not too firm. Serous exudates are rare, and, from the very nature of the lung lesion, can not be extensive.

Whether a desquamative process preceded the stage of exudation at present under consideration or not, there is now induced desquamation of the epithelial lining of the vesicles. The fibrin contracts, and free fluid collects in the vesicle or is taken up by the lymphatics. The red blood-cells undergo fragmentation, are broken up, and bronchial inflammation with some of the features of a bronchopneumonia occurs. The desquamated and fatty epithelium leads to liquefaction of the coagulum in the vesicle and to the conversion of the mass into an emulsion favorable for absorption or expectoration. These changes alter the color of the organ from red to gray, and the condition is spoken of as gray hepatization. The duration of the stage of red hepatization no doubt varies; in three days after the onset of symptoms the lung may be gray; on the other hand, the author has examined a lung thirty-nine days after the initial chill, and thirty-seven days after the clinical diagnosis of solidification, and found the organ still red.

Gray Hepatization.—When this stage is reached, the lung no longer resembles, in its gross appearance, the previous stage, just described. As indicated, the organ is reddish-gray, gray, or yellowish-gray, depending upon the degree to which the stage is developed; the organ is softer and less tense than in the red stage, tearing with the greatest ease, but is less readily broken by bending. The surface is moist and smooth on section, in contrast to the dry and rough surface observed in the red stage. (See Plate III.) In gray hepatization squeezing the organ leads to a rather free flow of the partly emulsified inflammatory exudate.

The peribronchial glands are enlarged, the pleurisy is more advanced, and occasionally the lymphatic channels, running from the pleura toward the mediastinum, are swollen and show as light yellow or yellowish-red streaks. The involved area is still airless, at least in the earlier stages of the gray change, as may be shown by the tests already given when considering the airless condition of the organ in red hepatization. Under the microscope no fibrin is to be demonstrated, but the vesicles are filled with cellular elements resembling those of bronchopneumonia; there are more leukocytes and desquamated epithelial cells in varying

stages of granular and fatty change, and there is less serum than in the bronchopneumonic exudate. The coagulability of the fluids that bathe the cut surface in the gray hepatization can be shown by thrusting the organ into strong alcohol, aqueous solutions of picric or chromic acid, or boiling water, thereby coagulating the albuminous constituents of the vesicular contents. The firmness and resisting density of the red stage can not, however, be redeveloped, as the material becoming solid at this stage is albumin undergoing coagulation, and not fibrin.

Terminations.—It is reasonable to suppose that the gray stage is the beginning process of resolution. The softened vesicular exudate, by fatty changes, eventually becomes transformed into an emulsion that is absorbable and sufficiently liquid to permit of being displaced from the air vesicles and expectorated. The amount leaving the lung by absorption may be in excess of that removed by expectoration, or the reverse. The amount of the exudate (estimated by weighing the normal lung and deducting its weight from that of the inflamed organ) varies for the entire lung between 1 kilogram and 1800 grams; by observing how little may be expectorated, the capacity of the absorbents can be, in part, appreciated. It is probable that this absorbed material is largely cared for by the lymphatics, as such exudates are not likely to pass through even capillary walls. The termination of lobar pneumonia in interstitial pneumonia will be considered with the latter. (See p. 593.) Occasionally, croupous pneumonia apparently terminates in tuberculosis. In such cases the tubercle bacillus may have been in the lung in some quiescent nodule, or the lesion may be the result of a secondary infection in the tissues weakened by the pneumonic process. (For the formation of abscess in lobar pneumonia see p. 575. Gangrene resulting from lobar pneumonia is also there described.)

Lesions That May Accompany Croupous Pneumonia.—*Pleurisy* is always present in a pneumonia that reaches the surface of the lung. Pleurisy of the base with pneumonia of the apex, inflammation of the opposite pleura, are combinations of pathologic interest. While the pleurisy is usually one of slight plastic or an abundant solid exudate and little serum, it is not invariably so; abundant serous exudates occasionally occur, and empyema (suppurative pleurisy) is not so infrequent as was once believed. It is now established that the pneumococcus is the essential etiologic factor in the various forms of pleurisy, and that it may, without mixed infection, induce suppuration is probable.

Pericardial inflammation accompanying pneumonia partakes of the same general characteristics already described as present in

pleurisy, and is due to the same cause. It occurs most commonly in pneumonia of the left lung, and especially when that part of the lung overlying the pericardium is the seat of the disease.

The blood changes that occur in croupous pneumonia, although not characteristic, are important. There is a notable increase in the number of finely granular oxyphile leukocytes; poikilocytosis is occasionally present; the alkalinity of the blood is decreased. Although not of unvarying import, increase in the leukocytes is considered a favorable prognostic omen.

The heart muscle may show cloudy swelling; less commonly, advanced granular change; and, rarely, a well-marked fatty degeneration may be in progress. Myocardial infective processes have not been observed. Cardiac thrombi on the left side develop rarely, except immediately preceding death, and when associated with endocardial inflammation. Just preceding death, in the agonal period, the slowed and greatly obstructed circulation of the right side may be embarrassed by clots extending from the right ventricle into the smaller ramifications of the pulmonary artery, and, at the postmortem, these may be pulled out as long tree-like or whip-like masses.

Endocarditis, both acute simple and acute malignant, occurs. The acute simple form has been found without the observer being able to demonstrate pneumococci in the blood or cardiac lesion; they are, however, commonly present. In the malignant form of endocarditis accompanying pneumonia the pneumococcus is invariably present, and in a small percentage of the cases the organisms of suppuration occur in the vegetations and blood.

Monarticular joint inflammations have been frequently noted, and are extremely likely to terminate in suppuration. It is interesting to note that pneumococci have been found in the affected joints, in the pus from the joints, and that arthritis has been induced by the intra-articular injection of the organism.

The extreme selection of serous surfaces by this organism and its products is further illustrated in the occasional *peritonitis* and inflammation of tendon sheaths that have been observed.

Meningitis is another illustration of the liability of serous surfaces to suffer; while it may occur with malignant endocarditis and be accompanied by embolic processes, both may be absent. All the intracranial serous structures may be the seat of the disease, or it may be restricted to a single fossa or region or to the base. Infection occurs through the blood or from the nasal or aural spaces, and the seat of the lesion may indicate the source of the infection. The process may be restricted to the meninges

or the brain structure may be involved. Involvement of the spinal meninges has been observed.

A number of mucous membranes that may be infected by the pneumococcus, either during pneumonia or independently; the most frequent are the ear (*otitis media*) and mucous surfaces of the nasal appendages: *e. g.*, *abscess of the frontal sinus*, containing the diplococcus and followed by a diplococcus-meningitis. *Suppurative parotitis* (the pus containing the diplococci) is occasionally observed. Fibrinous inflammations of the stomach, colon, and other mucous surfaces may occur; hemorrhagic and gangrenous processes are less frequent, except in the embolic phenomena which accompany malignant endocarditis. The epithelium of the mucosæ, liver, and kidneys is usually cloudy. The renal lesion in croupous pneumonia, manifested by the presence of more or less albumin in the urine, rarely passes on to an inflammatory condition which persists after the disappearance of the initial cause.

Bronchopneumonia.—This disease is also known as **lobular pneumonia**, a name objectionable in that it does not indicate the bronchial association that is always present, and also in the fact that embolic processes may be essentially lobular and still bear no relation in point of cause or pathology to the condition under consideration. The name **catarrhal pneumonia** indicates the character of the exudate, but not all of its component parts are catarrhal in point of origin, and the changes to be noted in the vesicular wall make the process more than a superficial inflammation. The designation **capillary bronchitis** is objectionable, as it does not indicate the accompanying vesicular change. The term *disseminated pneumonia* indicates the wide distribution of the process in contradistinction to the more or less circumscribed lesion of croupous pneumonia. The term *catarrhal bronchopneumonia* seems no better than bronchopneumonia alone. The various other synonyms that have been given in attempts to indicate the location or character of the lesion, the cause or termination, are either objectionable or obsolete.

Causes.—Bronchopneumonia is not, as a rule, a primary disease, but arises secondarily in some other process. In nearly all, if not all, the cases of this disease the bronchiole or the passage above is the initial seat of the lesion, and the vesicle is secondarily affected. When the inflammatory process follows disease of the intervesicular wall, such as tuberculosis of that structure, one can conceive the initial process to have been in the vesicle; but, aside from this factor, contiguous disease, bronchopneumonia, as the name indicates, begins essentially as a bronchial inflammation.

While no specific germ has been adduced, the phenomena are those commonly attributed to infection or infectious products. The pneumococcus of Fränkel is present in a relatively large percentage of the cases; it may occur alone or be associated with other organisms. The condition is so constantly a part of various infections that it would seem that the definite anatomic alterations to be described might arise from a multitude of causes, a few acting singly, or the combination of two or more factors. The fact that bronchopneumonia occurs most constantly, as an important process, in the young and the aged seems to indicate some peculiarity of tissue at those periods; this has been assumed to be, in part at least, an inability of the terminal air-passages to evacuate themselves, owing to the faulty or poorly developed elastic tissue in the lung of the young, or muscular weakness of the respiratory apparatus in the two extremes of life; further, the epithelium of the infant, in the transitional stages of development, is most abundantly thrown off as a result of an irritation that adult tissues would resist. That such excessive susceptibility of the mucous surfaces exists is shown in the gastro-intestinal diseases of childhood equally as much as in the pulmonary lesions. A similar susceptibility is manifest in old age.

Unsanitary surroundings, crowding, poorly ventilated sleeping or living rooms, are all predisposing elements. Exposure, cold, dampness, and other incidents of the winter months show a most marked influence, the disease being most prevalent from November to May, inclusive, reaching its acme in the uncertain, varying, climatic conditions of the early spring months. Its relation to the infections is shown in the constancy with which it develops in the presence of those conditions; of the acute infectious diseases, measles is the one with which it is most frequently associated, although diphtheria, both pharyngeal and laryngeal, especially the latter, is commonly the immediate precursor or accompanying lesion. Scarlet fever and whooping-cough are usually, and typhoid fever and smallpox may be, accompanied by bronchopneumonia.

When the respiratory apparatus is the seat of any of the specific infectious diseases, whether acute or chronic,—anthrax (as in wool-sorter's disease), tuberculosis, glanders, leprosy, etc.,—bronchopneumonia is extremely liable to occur; and when one of these processes involves the lung, catarrhal pneumonia is inevitable. The bacillus of tuberculosis in the lung, whether in the cavities of the alveoli, as when aspirated from above, or in the vesicular or bronchiole wall, as when brought by the blood or lymphatics, always incites a bronchopneumonia, which is modified

by the tubercular process, but is, nevertheless, a characteristic lesion. (See Tuberculosis of the Lung, p. 596.) In syphilis of the lung bronchopneumonia may be present.

When infectious materials are drawn into the lung, as in the deglutition and aspiration pneumonias, to which reference has already been made, bronchopneumonia and other accompanying infective processes ensue; that bronchopneumonia is not the whole of the process is shown by the frequency with which suppuration or gangrene may follow. (See Pulmonary Suppuration, p. 574.) Bronchopneumonia also terminates fibrinous or lobar pneumonia when resolution is gradually reestablishing the normal.

In conclusion, it remains to be said that any condition that lowers the vitality of the individual, that weakens the avenues open for infection, that depresses or debilitates, favors the development of bronchopneumonia. To this group of causes belong Bright's disease, chronic heart disease, convalescence from acute processes, or the debilitating influences of more chronic ones. Bronchopneumonia always accompanies, to a varying degree, pneumoconiosis.

Morbid Anatomy.—In recent cases, acute in time, the lung is more voluminous than normal, and does not collapse with usual promptness, and may not shrink in the least when the chest is opened; there is not that dense firmness of the tissue involved, so constantly present in fibrinous or lobar pneumonia, and on superficial examination the lung appears to crepitate throughout; examined more closely, areas that do not crepitate are easily found; while firm, they are not dense, and are small nodules in contrast to the large areas of fibrinous pneumonia. On the surface of the lung near the base, as a rule, are areas sunken below the surface, blue or bluish-brown in color, usually isolated and small, although in rare instances almost, if not quite, all of a lobe may be involved in the atelectatic process. Usually, such areas can be reexpanded by forcing air into the bronchus. The area joining that of collapse is not uncommonly emphysematous, as are the anterior and apical margins. At scattered points will be found projecting areas, over which the pleura may be rough or even show a beginning exudate. On section, the surface is usually dark or reddish, although in adults it may be gray at points, not unlike the gray stage of fibrinous pneumonia. The surface is smooth and moist, and drips blood or bloody serum. The outline of the affected lobules can be seen, or, where a number have run together, they will usually be found in different stages, and can in that way be made out. A suitable lobule, on longi-

tudinal section, shows the grape-like structure of the lung, with alveoli, infundibula, and bronchiole filled with puriform mucus; a transverse section reveals the central bronchiole, containing a tenacious plug of mucus, surrounded by distended vesicles and the adjacent collapsed lobules. Adjoining the inflamed area the areas of collapse may be well made out, or they may be indistinct; if defined, they are dark, smooth, airless, and instead of bulging when cut, apparently retract; when immediately subpleural, there may be ecchymosis in or over them; when not well defined, the outline will show as darkish bands traversing the lobes in an irregular manner. The peribronchial lymphatic glands will be, not uncommonly, swollen and edematous, owing to the effort made to carry off the degenerative product of the bronchial and vesicular inflammation.

Morbid Histology.—If a drop of the fluid that fills the air-spaces be squeezed out upon a slide, it will be found composed of germinal, granular, and fatty epithelium, with a varying number of leukocytes, rarely any red blood-cells. The fluid exudate must be solidified before making sections for histologic examination; this may be accomplished by thrusting a part of the affected tissue into boiling water, and thus coagulating the albumin in the serum and incarcerating the cellular elements; such a process alters the surrounding structures too profoundly to be commendable, and the same object may be secured by using absolute alcohol or Flemming's or Hermann's fixing solutions. (See pp. 48 and 49.) Infiltration is imperative in order to retain the histologic structure in place.

Examination of properly prepared sections will show the alveoli filled, not with a fibrin-bearing exudate, as in lobar pneumonia, except in a very few scattered vesicles, but a mucoid exudate containing the cellular elements previously indicated, the epithelium being especially predominant. The bronchiole lumen will be found occluded by the same exudate, and the wall infiltrated by young cells, its integral elements pushed apart, typifying the swelling that was present. Longitudinal sections reveal, in the bronchiole, more or less irregularity in the transverse diameter—saccular dilatation. The infundibulum and its surrounding vesicles are filled with a similar exudate, and the same cellular infiltration of the vesicular walls may be found. Toward the margin of the affected lobule the distention will be less marked, and the alveolar epithelium will show desquamation and marked fatty changes. The capillaries of the walls, both vesicular and bronchial, will be found distended and surrounded by leukocytes. The lymphatic channels leading from the affected

areas are usually engorged. In the peribronchial lymphatics more or less swelling and infiltration are manifest.

In the bronchopneumonia accompanying the aspiration of foreign bodies into the bronchi the bacteria present infiltrate the connective tissue, abundant leukocytic infiltration occurs, and, if the processes have sufficient time, suppuration or gangrene may ensue.

Terminations.—Acute bronchopneumonia undergoes resolution rapidly once the process begins; upon the withdrawal of the cause the lymphatics and blood-vessels care for the unexpectorated exudate, epithelium rehabilitates the denuded walls, and organization of cellular products in the vesicular and bronchiole walls follows the removal of the liquid exudates that caused the swelling to which reference was made while considering the his-

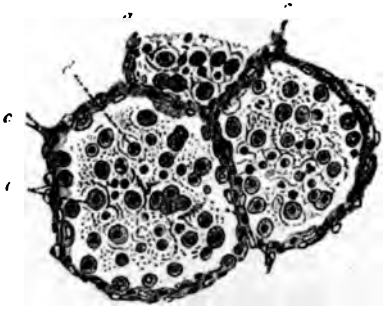


FIG. 276.—TWO ALVEOLI AND A PART OF A THIRD FROM LUNG IN CATARRHAL PNEUMONIA. *a, a, a.* Walls of the alveoli. *b.* Desquamated epithelial cells from the walls of the alveolus. *c.* Alveolus filled with catarrhal exudate. *d.* Leukocyte.

tology. The feebleness of the respiration and the reduced resistance may enable deposited bacteria to secure a more or less permanent abode. That pyogenic and saprophytic bacteria may induce suppuration and gangrene, as has already been stated. In the distended vesicles or lobules tubercle bacilli may lodge, and the characteristic phenomena of tuberculosis ensue, constituting a tubercular infection secondary to the bronchopneumonia. This, while possible, is no doubt rare, and where caseation with fibroid encapsulation of the caseous area is found postmortem, it is probable that the disease was tubercular from the start, but that the conservative elements limited the process; these areas may become calcareous, and exhibit the other phenomena so constantly associated with quiescent tuberculosis. It is possible for the tubercle to follow by a more wide-spread infiltration, or a wide-

spread infiltration of tubercle may have induced the bronchopneumonia. At one time it was believed that caseation and fibroid change were a legitimate termination of bronchopneumonia, and recognized as a frequently occurring condition. While, as already stated, one can conceive of a simple nontubercular area of consolidation becoming fibroid and limited, independent of the bacillus of tuberculosis, still when caseation and calcareous infiltration are found, the evidence is clearly that of a "healed-in" tuberculous focus.

Interstitial pneumonia, chronic interstitial pneumonia, *pulmonary cirrhosis*, or, more properly, *pulmonary sclerosis*, *fibroid induration*, *fibroid lung*, with various other synonyms, is a chronic productive inflammatory process, involving essentially the connective tissue of the organ, with increase of the fibrous elements and more or less contraction of the newly formed tissue. The degree to which the change may progress is dependent upon many factors, and the fact that the process is secondary to other conditions has led to a multitude of names, each assuming a separate condition. No inflammation of the lung tissue, no invasion of the pulmonary structure by foreign bodies, whether coal or iron, bacteria or morbid growths, is likely to occur without a certain amount of increase in the fibrous tissue. This statement indicates the causes which are active. Fibrinous pneumonia, bronchopneumonia, tubercular pneumonia, and other infectious processes which may induce inflammation,—as syphilis, leprosy, and actinomycosis,—pneumoconiosis, and inflammation of the pleura, may all be cited as etiologic factors.

The fibroid change in the lungs may involve only a small area, as when the cause is limited to that point; thus, a small, circumscribed, possibly quiescent tubercular process in an apex may be surrounded by a marked area of interstitial fibroid change. When a protracted bronchopneumonia has involved, for any great length of time, the entire pulmonary structure, increase of fibrous tissue will be present throughout both lungs, the bronchial walls will be thickened, and every intervesicular septum more or less fibroid. Attempts have been made to classify these various stages and degrees, but one lung may be in one stage and the other show similar lesions to quite a different degree; one lung may be universally fibroid, the other show only points of fibroid change—the so-called local fibroid pneumonia. As to source or cause, the fibrous-tissue increase follows out certain lines.

In fibrinous pneumonia the area involved may not undergo resolution, but pass into this condition of fibroid change. The connective-tissue cells in the vesicular wall proliferate, and the

fibrinous plugs occupying the vesicles and infundibula pass through the various stages of embryonic and granulation tissues, and eventually the mass becomes converted, more or less completely, into fibrous tissue—a condition spoken of as *gray induration*. The area is gray, firm, elastic, and smooth, and looks not unlike recently developed but slightly contracted connective tissue. The process is one of the rarest terminations of croupous pneumonia. In persistent bronchopneumonia the inflammatory changes, already noted as occurring in the vesicular wall, lead to thickening, and in the areas of collapse this may preclude the reestablishing of function. The most marked development of fibrous tissue occurs around the bronchi,—a peribronchitis,—followed by the fibrous invasion extending to the septa between lobules, and eventually to the vesicular walls.

When fibroid lung follows an inflammation of the pleura,—*pleurogenous interstitial pneumonia*,—the condition is usually associated with plastic pleurisy, the formative inflammatory process extending into the lung by involving the interlobular septa. This differs etiologically from the fibroid condition already described as occurring in the more or less completely collapsed lung with thickening of the pleura and the binding down of the lung by an interstitial process; the shrinking or contraction of the lung is secondary to the development of new fibrous tissue; in the collapsed lung the fibroid change is secondary to the pleural thickening and the cessation of function.

The development of fibroid lung in pneumoconiosis has already been referred to (see Pneumoconiosis, and other infiltrations of mucous membranes, p. 533; also chronic catarrhal inflammation of mucous membranes, p. 539), and it remains only to be said that the increase in fibrous tissue there noted is due to the direct influence of the foreign bodies in the connective tissue of the lung, exactly as fibrous tissue develops around any extraneous body in the process of "healing-in"; to this must be added the thickening incident to the accompanying inflammation of the mucous surface, such as always occurs when persistent inflammation leads to fibrous changes in the submucosa. (See Fig. 264, p. 540.)

Morbid Anatomy.—From the foregoing it will be seen how varied the appearance of such organs must be. In the simpler, less extensive, and generally disseminated lesion the organ will be firmer than normal, and may show on the pleura the fibroid areas between lobes or lobules. On section, these areas of fibrosis appear as gray, more or less pigmented masses, usually radiating from the central bronchus along the lines of the interlobar or interlobular septa. The uninvolved portions of the lung

may be slightly emphysematous, and the elasticity of the organ so modified that it collapses slowly, if at all. In more advanced cases, or more marked fibroid change, the fibrous tissue involves a whole lobe, or a greater part of a lobe, and is conspicuous; on section, it differs but in degree from the next condition to be described, in which the whole of a lung is involved.

This constitutes *true cirrhosis*, or, better, *sclerosis of the lung*. Of necessity, the process is unilateral, and the corresponding chest-wall shrunken and pulled in, and the shoulder lower than that of the unaffected side. The opposite lung is voluminous, extends far past the median line, is emphysematous, and the mediastinal tissues, heart, and great vessels are displaced toward the affected side. The volume of the fibroid lung may be incredible; the author saw a case in which it was not larger than two small fists, and Osler speaks of a case in which the affected organ was not found (!). The lung is firm, at times doughy and airless, and resists the knife to an unusual degree. In the pleurogenous form, and when the process follows fibrinous pneumonia, the pleura may be adherent, and is always very much thickened; if the condition arose purely intrapulmonary, the pleura may not be affected. The bronchi are nearly always more or less dilated, sometimes to an enormous degree. (See Bronchiectasis, p. 563.) The cut surface shows the fibroid character to advantage; the blood-vessels and bronchi are embedded in the mass of grayish tissue. The slowness of the circulation and the loss of functional activity in the affected organ renders infection readily possible; rarely, this may be pyogenic, and leave a cavity. Tuberculosis as a cause and tuberculosis as a sequence—an infection of a point of least resistance, as this truly is—occurs in no small number of cases; what relation the tuberculous process bears to the interstitial change can usually be inferred by the location and character of the lesion. The cases of tubercular origin usually show an apical cavity and some lesion of the opposite lung.

Morbid Histology.—This has been largely considered in the preceding, and varies as does the gross anatomy. In the less marked cases fibrous tissue in varying stages of development may be found in the vesicular walls and around the bronchi; in the advanced cases—those last considered—the bands of fibrous tissue have compressed and obliterated the pulmonary vesicles, and have converted the areas involved into irregularly outlined masses of cicatricial tissue. A varying amount of catarrhal inflammation may be evident in the vesicular structure or the change indicative of a past catarrhal process may remain. Evidence of tubercu-

fibrinous plugs occupying the vesicles and infundibula pass through the various stages of embryonic and granulation tissues, and eventually the mass becomes converted, more or less completely, into fibrous tissue—a condition spoken of as *grey induration*. The area is gray, firm, elastic, and smooth and looks not unlike recently developed but slightly contracted connective tissue. The process is one of the rarest terminations of croupous pneumonia. In persistent bronchopneumonia the inflammatory changes, already noted as occurring in the vesicular walls, lead to thickening, and in the areas of collapse this may preclude the reestablishing of function. The most marked development of fibrous tissue occurs around the bronchi,—a peribronchitis,—followed by the fibrous invasion extending to the septa between lobules, and eventually to the vesicular walls.

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losis can often be demonstrated microscopically when the grosser lesions are lacking.

Termination.—Under the most favorable circumstances, in non-tubercular cases, arrest of the process is all that can be expected. This is dependent upon the possible removal of the cause. In a vast majority of cases tuberculosis terminates the case. The limited fibroid change—local interstitial pneumonia—around a point of tubercular infection may be beneficent in that it is possible to limit the dissemination of a localized tubercular infection, and the increase of connective tissue with calcareous infiltration, as so often occurs, is no doubt the local reaction to an infection by which dissemination is prevented.

Tuberculosis of the lung is manifested in a number of ways, depending upon the resistance of the individual, the virulence of the infecting organism, and the route of the infection, as well as upon the extent of bacterial distribution in the pulmonary tissue. It is, of course, in all its forms due to the tubercle bacillus. The organism may reach the lung through at least three avenues: (1) bronchi, (2) lymphatics, (3) blood-vessels, and possibly by direct invasion from adjacent tissues.

Pneumatogenous infection occurs through the inhalation of tubercle bacilli. It is probable that where the bacilli are deposited within the larger bronchioles, invasion of the peribronchial tissue is less likely to occur; and that when the tubercle bacilli escape extrusion by the activity of the ciliated epithelium and by expectoration, they may pass through the denuded areas in the bronchial wall, reaching the peribronchial tissue, and eventually a lymphatic gland, in which they tend to induce tuberculosis. In other instances a primary tuberculous lesion may arise in the larynx, trachea, or larger bronchi, and from this invasion of the lymphatic glands may occur.

From a primary tuberculous focus in the larynx, trachea, or larger bronchi, or from a tubercular area in the lung, infected material may be aspirated into the smaller bronchi, or even into the vesicular structure. It is probably more common for the organism to reach the finer ramifications of the bronchioles when inhaled in the form of a fine dust. No matter how the organism reaches the vesicular structure or the smaller bronchioles, a catarrhal inflammation results. At first this inflammation partakes of the characteristics of an ordinary catarrhal process associated with desquamation of the epithelium and with accumulation of the catarrhal products in the vesicle, infundibulum, and smaller bronchiole. Within this inflammatory collection growth of the tubercle bacilli is favored; instead of the catarrhal

accumulation undergoing the usual softening and expulsion, caseation results, due to the specific action of the product of the tubercle bacillus. The progress that the change makes must depend largely upon the virulence of the organism and upon the susceptibility of the individual. It is probable that, with a high degree of immunity, the bacillus may be destroyed at once, and that the bacterial invasion of the vesicular wall may be arrested by the protective forces of the tissues.

When infection through the bronchi occurs, as just indicated, it is not necessary to presuppose any antecedent lesion. In a small percentage of cases, however, a bronchopneumonia, not of tubercular origin, is infected by the tubercle bacillus. The result is essentially the same as though the lesion had been tubercular from the start. Under favorable circumstances the inflammation

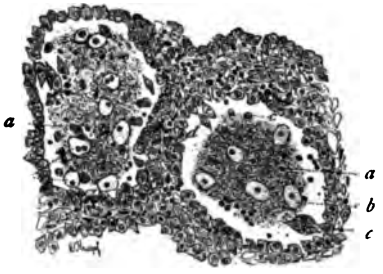


FIG. 277.—TUBERCULAR PNEUMONIA. THE DESQUAMATIVE LESION WITHIN THE AIR VESICLES, WHICH OCCURS NEAR TO AND AROUND TUBERCLES IN THE LUNG, OR RESULTS FROM THE DEPOSIT OF THE TUBERCLE BACILLUS IN THE AIR VESICLES.—(*Schmaus.*) × 250 diameters.

a, *a*. Exudate undergoing degenerative changes (caseation) in the air vesicle. *b*. Round cells in same. *c*. Desquamating cells. The intervesicular walls are thickened.

is restricted to a small area of pulmonary tissue. The solidified nodule, commonly small, undergoes caseation and encapsulation by a wall of fibrous tissue, into which lime salts may be infiltrated. This constitutes the so-called quiescent, "healed-in," or cretaceous tubercle, and is what the older writers called chronic or caseous catarrhal pneumonia. With less evident resistance, or with more virulent infection, involvement of the bronchioles and of adjacent vesicular structures occurs. This is commonly preceded by more or less leukocytic invasion and proliferative change, which later terminates in necrosis and caseation. The process more or less rapidly involves the whole of the lobule in which the original infection occurred. When a lobule or part of a lobule has been infected, the area may be enlarged by the coalescence of adjacent

lobules simultaneously involved, or it may extend from lobule to lobule.

The gross lesion resulting from such infection must vary. As a rule, in adults the lesion involves to a greater extent and is most conspicuous in the apex, although the lower lobes may also suffer. The point in the apex usually involved is from two to five centimeters below the superior border. Of the many explanations that have been presented for the well-known frequency with which the apex is involved, none is fully satisfactory. It is probable that the more active circulation and freer movement of the lower part of the lung may better enable the organ to expel the infectious material, and, by reason of its abundant blood supply, to resist infection. The lessened pulmonary movement at the apex offers better opportunities for the settling, if one may use that term, of infectious material on the bronchial surfaces. In adults involvement of the lower lobes is usually indicative of a primary lesion higher in the lung, from which the infected material has been aspirated into the more dependent portions.

In many instances of pneumatogenous tuberculosis the process remains local, with the development of fibrous tissue in the surrounding structures, to which reference has already been made. In other cases the initial infection must have involved a number of areas in the pulmonary tissue, or a primary infection may have been followed by extension to adjacent lobules. These recognized differences possibly justify the terms (1) *localized, restricted*, or *chronic pneumatogenous* or *bronchogenic tuberculosis;* and (2) *disseminated, bronchogenic, tuberculous pneumonia.* The symptomatology of the conditions is vastly different, largely because of the greater amount of pulmonary tissue involved in the last-named process, but pathologically there is little difference except that due to the fact that the sudden appearance of a multitude of lesions must be taken as an evidence of weak resistance, and as this must of necessity further lessen the protective powers, the disease not uncommonly terminates rapidly. With the inception of the initial lesion of tuberculosis in the pulmonary tissue, extension to adjacent intervesicular and interlobular structures occurs by means of the lymph paths, constituting a form of *lymphogenous* or *lymphogenic tuberculosis.* Thus, in many areas of purely bronchogenic tuberculosis of the kind described in the foregoing pages, it is quite easy to recognize that the extension is taking place by means of the adjacent lymphatics. This view is further supported by the fact that the lymph paths through the pulmonary tissue are followed, and that eventually the lymphatic glands are

involved. Involvement of a lymphatic lying close to a blood-vessel, pulmonary artery, or vein may be followed by extension into the vessel-wall, which later becomes caseous. In the vessel may be formed a thrombus in which caseation occurs, followed by the pouring of infectious material into the blood stream. If the blood-vessel involved be small, and the blood current be toward the periphery, as would be the case in the branches of the pulmonary artery, there is brought about a circumscribed *hematogenic miliary tuberculosis*. In other cases the infection of the pulmonary tissue through the blood stream is more uniform, as the result of a wider and more general distribution of the tubercle bacilli deposited from the circulating blood. In the circumscribed hematogenic tuberculosis one lung or a part of a lung may be involved, while in the general or diffuse hematogenous (miliary) tuberculosis there is usually a more or less uniform involvement of both lungs.

Morbid Anatomy.—There is probably no other well-known affection of the lung associated with more diversity in the gross lesions, and due, in all its forms, to the same cause. In some of the cases it may be possible to formulate an opinion as to the method by which infection occurred. In other cases this is quite impossible. Usually, it is said that, anatomically, tuberculosis of the lung manifests itself in three forms: (1) An acute miliary tuberculosis, also called acute phthisis, or galloping consumption; (2) chronic ulcerating or caseous tuberculosis; (3) fibroid phthisis.

The morbid anatomy of **acute miliary tuberculosis of the lung** must depend upon the extent and duration of the tuberculous process; organs in which there has been a wide-spread distribution of a large number of tubercles will not show the same changes as those in which there has been a more restricted area of involvement, with fewer tubercles. Sometimes the large number of tubercles, with the associated proliferative changes, may almost as fully solidify a lung as croupous pneumonia, and, both clinically and pathologically, the organs may closely resemble each other. If the process has existed for even a comparatively short time, the miliary tubercles become sufficiently large to be easily recognized, and, of course, as soon as this occurs the anatomic diagnosis is easily made. The lung is more voluminous than normal, and does not collapse with its wonted readiness. The pleura is frequently the seat of an old inflammation, and not uncommonly shows uniform adhesion between the visceral and parietal layers. Small tubercles may be seen in the pleura or just beneath, or, what is more common, they are palpable. On inci-

sion, the lung usually cuts with more resistance than normal. The amount of moisture is dependent upon the presence of an associated edema, intense congestion, or hyperemia. The recognizable tubercles are usually paler than the surrounding lung tissue, and are white, grayish-white, or yellow in color. (See Tuberculosis, p. 366, also Morbid Anatomy of Tuberculosis, p. 368.)

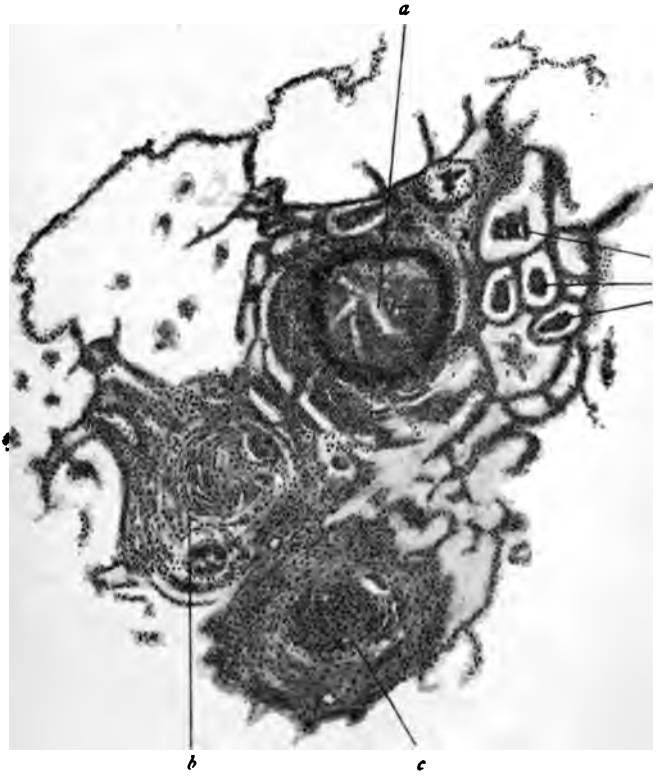


FIG. 278.—TUBERCULOSIS OF THE LUNG.

Tissue fixed in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin, and mounted in balsam. *a*. Tubercle with advanced caseation. *b* and *c*. Tubercles showing less advanced degenerative changes. In the upper and right quadrant of *b* is seen a giant cell. *d*. Three air vesicles partly filled by inflammatory products, tubercular pneumonia. (¼-inch objective, 1-inch ocular.)

With the acute lesion, evidences of older tuberculosis may be present, such as healed-in areas, areas of caseation and fibrosis, or fully formed cavities. It may be possible to demonstrate the primary nodule from which infection has occurred, although in the large majority of cases the demonstration will be unsatis-

factory, and seldom conclusive. An examination of the lung during the period at which the tubercles are forming, or when they are fully formed, will result in the recognition of histologic changes such as shown in figure 228, page 370. (See, also, Fig. 278.) In acute cases there is usually considerable catarrhal pneumonia or intravesicular exudate, and sometimes this may be fibrinous, further explaining the gross resemblance of the lesion to croupous pneumonia.

Morbid Anatomy of the Chronic Ulcerating, Ulcerative, or Caseous Tuberculosis of the Lung.—This is a type of the disease that usually follows pneumatogenous infection. The lesions are more commonly situated in the apex, although other parts of the lung may be involved. The lesion consists for the most part of caseous areas, varying in size from purely microscopic bodies (miliary tubercles) to cavities from five to ten centimeters in diameter. The cavity formation is brought about by caseation and confluence of a large number of tubercles, with an associated bronchopneumonia, which itself becomes caseous, and is, of course, due to the tuberculous infection of the pulmonary tissue. As these areas of caseation are increased in size by peripheral extension and coalescence, obliterative change takes place in the blood-vessels, the vesicular walls and fibrous septa break down, the pulmonary tissue itself becomes caseous, and eventually the necrotic collection ruptures into a bronchus. With evacuation of the caseous contents a cavity is formed. The wall of such a cavity is lined by a layer of necrotic and caseating pulmonary tissue containing tubercles in various stages of caseation, and the inflammatory products that usually accompany infection by the tubercle bacillus. External to the caseous layer is a wall of granulation tissue composed largely of lymphoid cells, and usually containing easily recognized tubercles. Outside of this layer there is a variable amount of fibrous tissue.

The most disastrous changes in pulmonary tuberculosis result from *secondary infection by pyogenic organisms*. Whether such organisms find ready access to the caseous area before its rupture into the bronchial wall or not, their introduction is assured by this time, and hence there are added to the tuberculous process, properly so-called, active pyogenesis and the absorption of the products of pyogenic bacteria. The gradual extension of the caseous tuberculosis is favored by the occurrence of mixed infection. Necrotic changes in the contiguous tissue and involvement of the adjacent lymphatics may progress slowly. In other instances there is a more rapid extension, and, after a comparatively short period of cavity formation, invasion of a

blood-vessel or prominent lymph canal occurs, or the process extends to other parts of the lung, leads to the rapid dissemination of infection and to death.

Morbid Anatomy of Fibroid Phthisis.—The term fibroid phthisis is applied to tuberculous processes involving a lung where the tendency is toward fibrosis, restriction, limitation, and healing-in, and where necrosis, degeneration, and extension are limited by the protective powers of the tissues or are rendered less liable to occur

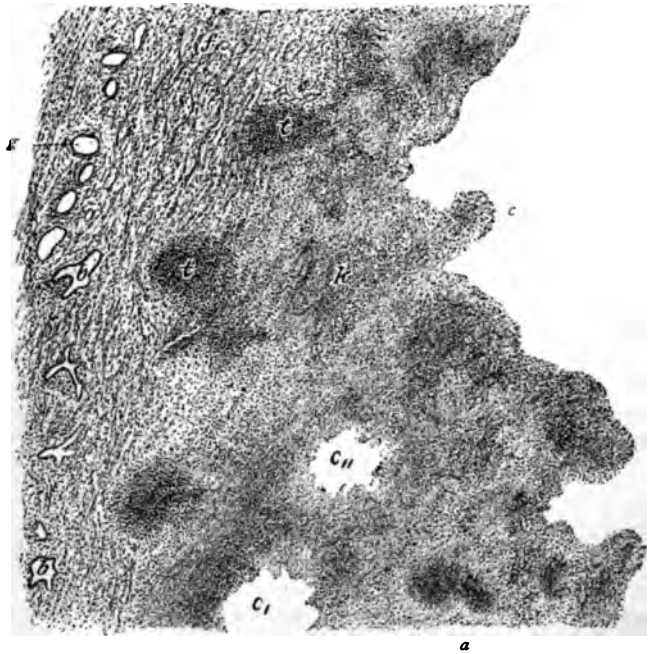


FIG. 279.—WALL OF A TUBERCULOUS CAVITY.—(*Schmaus.*) × 100 diameters.

c. Cavity. *c'*, *c''*. Smaller cavities that will, eventually, as the result of caseation and liquefaction of the intervening tissue, blend with the larger cavity. *b*. Remains of a bronchus. *t*, *t*. Tubercles undergoing softening. Just over *a* are shown other tubercles. *k*. Caseous wall. *g*. Blood-vessel.

by reason of reduced virulence of the infecting organism. In typical cases a comparatively small area of the lung is involved. In the purely tuberculous lesion a large portion of the lung may show the changes of fibroid pneumonia. In other cases the evidence of tuberculosis, at present active or quiescent, may be irregularly distributed through a large amount of the pulmonary tissue. In typical cases the evidence tends to indicate that

tuberculosis is being limited or restricted by fibroid and calcareous changes : in other words, that healing-in is progressing. In patients dying from other causes small areas are not infrequently found in which the tuberculous process has been fully restricted or walled off by masses of fibrous tissue, or limited by calcareous infiltration. (See Quiescent Tuberculosis, p. 370.)

In a large percentage of the cases of tuberculosis of the lung, as observed postmortem, the disease is manifested by mixed lesions, due to the presence of more than one form of tuberculosis, as described in the foregoing pages. There is not infrequently a distinct area of old cretaceous tubercle. Around this, at times some distance from it, will be recognized a more recent and active tuberculosis, with cavity formation, and corresponding to the anatomic subdivision—chronic caseous tuberculosis. Still other parts of the lung may show the changes of a typical acute miliary tuberculosis.

Syphilis of the lung occurs in both the *congenital* and *acquired* forms of the disease. In the former a condition known as *white hepatization* is occasionally seen ; proliferation of the cells that line the fetal vesicles and the connective tissue of the walls leads to the obliteration of the air-spaces, and when the inspired air, at birth, enters the lung, none gains ingress to the affected area ; the only circulation to this part is that for supplying nourishment ; hence, the area is pale, anemic, and is said to show *white hepatization*, the paleness contrasting with the surrounding hyperemic area. Another manifestation of transmitted syphilis is the ordinary gumma. This may be found in any part of the lung, but is usually near the larger bronchi at the hilum. The gummata are for the most part small, but they may attain diameters of from two to six centimeters. Gummata of the lung in congenital syphilis are of infrequent occurrence, but when fully developed, they do not differ from those found in the acquired disease.

In *acquired syphilis* gummata are more frequent ; the situation is usually at the root of the lung, but they may be anywhere. They are gray or grayish-yellow, not uncommonly caseous, and surrounded by a fibrous capsule, which, if recent, is translucent ; if older, is firm, truly fibroid, and dense. Like all the infective granulation tumors, these begin in the alveolar walls or in the walls of the bronchi, beneath the basement membrane ; after the aggregation of cellular elements hyaline degeneration ensues, and eventually caseation completes the process, and evacuation into a bronchus may follow.

Occasionally, an interstitial pneumonia accompanies the formation of the gumma, and Virchow believed that a purely syphilitic

process may begin as an interstitial inflammation at the root of the lung and extend along the course of the interlobar and the interlobular septa, particularly the latter. When marked, it may be attended by bronchiectasis and all the usual phenomena of interstitial pneumonia.

Leprosy of the lung may occur as a distinctly miliary process, the leprous nodules so closely resembling those of tuberculosis that many claim that the determining factor is a tubercular infection of a leprous individual; and the almost utter impossibility of differentiating the lesions has led a few to believe that leprosy was but a form of tuberculosis; evidence confirmatory of this view is not in the least conclusive, and for the present there seems to be no reason for believing that the two diseases are in any way related.

Glanders of the lung may arise as the result of aspiration of the bacilli from lesions higher in the passage, or, as in acute glanders, the infection may occur by the blood stream. Once localized in the lung tissue, whether interstitial or intravesicular, a more or less severe bronchopneumonia is brought about, and frequently this proves fatal. When time is afforded, the typical glanders nodules develop. These lie, as a rule, immediately under the pleura, and present somewhat different aspects at different stages of their development. At first they are gray, slightly translucent, and much softer than tubercle; later they become somewhat denser, and hyaline change occurs in the center, eventually terminating in a caseous-like, encapsulated mass, especially if the process be restricted to one or two points of infection in an animal not very susceptible to the disease. In the horse, in which animal susceptibility is marked, and occasionally in man, the condition is likely to terminate in a suppurative pneumonia by pyogenic infection of the glanders nodules.

Actinomycosis of the lung results, in most cases, from infected material reaching the part involved through the air-passages; a bronchial inflammation accompanies the fungus down into the lobules, where a so-called miliary bronchopneumonia ensues; the number of these areas is dependent upon the number and dissemination of the fungi. A mass of granulation tissue develops around the point of infection, in which also occur characteristic groups of fungi. Suppuration ensues, and not uncommonly cavity formation; it is claimed that the ray fungus is itself pyogenic, and can, therefore, induce pus-formation without the intervention of the cocci of suppuration. When the actinomycotic lesion approaches the surface, an adhesive pleurisy usually results, and progresses to obliteration of the

cavity. Flexner has reported an instance in which the suppurative process penetrated the chest-wall and the diagnosis was made by finding the characteristic granules in the discharge. Mediastinal actinomycosis may or may not accompany the pulmonary form, or the one may be secondary to the other. Occasionally, actinomycotic fibroid changes in the lung and "healing-in" of the area infected may occur. In such cases the masses found postmortem are surrounded by a dense fibrous and calcareous capsule. The diagnosis of actinomycosis, both clinical and pathologic, is dependent upon finding the fungus in the sputum during life or in the masses postmortem. (See p. 161.)

Tumors of the lungs are rarely primary; usually, they arise by metastasis from other organs or by invasion from adjacent structures. The primary tumors are rarely of the adult epithelial type; adenoma of the bronchial glands has been described. The embryonic epithelial tumors are not correspondingly rare. It has been the author's fortune to see, within a few months, three specimens of primary cancer of the lung. When carcinomata occur in the lung, as the result of the rich vascular supply and the relatively small amount of connective tissue, the neoplasm is most commonly encephaloid. The growth may be circumscribed and manifest itself as a few masses, or it may be but one gray or white, soft nodule. Each nodule may develop as a single mass without very marked dissemination, but more commonly extension occurs through the lymph-channels, and the nodules become disseminated throughout the lung tissue. The local metastasis gives rise to nodules similar to the original, which, by extension, run together and convert nearly all, if not all, the lung into a cancerous mass. Invasion of peribronchial and mediastinal lymphatics takes place, and if not fatal by this time, the process may extend to the opposite organ.

Primary tumors of the adult connective-tissue series are less frequent. *Fibroma*, *chondroma*, *osteoma*, and mixed forms of these, with, rarely, a small quantity of *lipomatous* tissue, have been described. They are commonly multiple; usually, a number are to be found disseminated throughout one or both lungs.

Embryonic connective-tissue tumors (*sarcomata*) are infrequent primary tumors of the lung. The form of sarcoma known as *endothelioma*, arising in or from the pleura, is the most frequent. Like the cancers, they usually form a single large mass, but may extend to the glands and mediastinal tissues. Sarcoma as a primary tumor is restricted to one lung.

Secondary tumors of the lung arise as the result of invasion through the lymphatics or the blood; even the instances of ap-

parently direct invasion are not truly so. The embryonic epithelial tumors—the cancers—involve the lung as secondary growths in a very small percentage of the cases of carcinoma elsewhere. The epitheliomata rarely, if ever, the scirrhus more commonly, and the encephaloid most frequently, occur as secondary growths in the lung. The cancers, spreading by the lymphatics, usually involve those structures in the lung first, and manifest dissemination along the course of the lymphatic channels. Reaching the pleura by the lymphatic system, dissemination may occur along the course of the interlobular lymphatics, in which will be seen the grayish cancerous lines traversing the connective-tissue septa, and even extending to the peribronchial glands.

Carcinoma occasionally reaches the lung by the blood, and the frequency with which this is associated with an initial focus in the digestive organs, more especially that part of the alimentary canal that communicates with the chyle duct, apparently explains this form of dissemination; in reality, the cancer cells have reached the blood by being poured into the venous circulation through the lymph-channels of the abdominal cavity. When a cancerous embolus lodges in the lung, the growth immediately proceeds in the usual way; as these emboli are most commonly multiple and are fairly abundant, both lungs are likely to be involved, and many small tumors occur more frequently than a single large one. There can be found, of course, no regularity in their location, and, once lodged, they follow the same processes of growth and local dissemination that has already been indicated; the encephaloid cancer is the one most frequently reaching the lung by metastasis; encephaloid cancers that have undergone colloid or mucoid change are especially liable to such dissemination. Scirrhus rarely involves the lung.

Of the secondary tumors belonging to the adult connective-tissue series it is said that chondromata and osteomata may reach the lung. Sarcomata (embryonic connective-tissue tumors) are the most frequent invaders, by metastasis, of the pulmonary tissues. This is due to the relation which the cellular elements of such a tumor bear to the blood channels which course through it. The small round-cell varieties are those most commonly noted, although any form of sarcoma may invade the lung. As to the seat of the initial growth, it is found that the sarcomata arising in bone, and especially in the long bones, are the most frequent as secondary growths in the lung. Melanotic sarcomata are also prone to such metastasis. Unlike cancers, sarcomata,

if situated in the distribution of the portal vein, rarely reach the lung, but, traveling by the blood-vessels, involve the liver.

Parasites in the lung and bronchi are not of frequent occurrence. Reference has already been made to the distoma westermanni, distoma pulmonale, or bronchial fluke, as a cause of hemoptysis. (See p. 567.) Ascaris lumbricoides occasionally migrates into the air-passages, and may cause obstruction with fatal results; or, reaching the bronchi, may induce gangrene, etc. It is not uncommon in infested bodies to find that the worm has entered the air-passages postmortem. *Hydatids* occur in the lung; they may be central or subpleural. The subpleural form and hydatids of the pleura may occur together; in either case effusion into the pleura is usually found, and not uncommonly empyema. The cysts are multiple, and commonly are near the base. They may be diaphragmatic. When in the lung, the compression resulting from their growth leads to conditions favorable to infection, and abscess and gangrene may result. Clinically and pathologically, a positive diagnosis is dependent upon finding the hooklets in the cysts or discharges. (See p. 206.) The parasites more rarely found in the lung are the cysticercus cellulosæ, strongylus longevaginatus, pentastoma denticulatum, etc.

CHAPTER IX.

URINARY ORGANS.

Normal Structure of the Kidney.—The kidney varies somewhat in size: normally, it weighs between 170 and 210

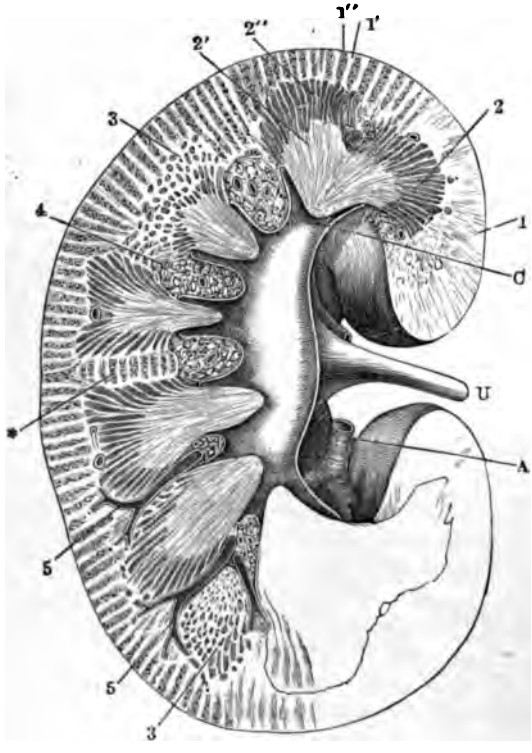


FIG. 280.—LONGITUDINAL SECTION OF THE KIDNEY.—(*Tyson, after Henle.*)

1. Cortex, equal in thickness to about one-half the length of the medullary pyramid. 2. Medulla. C. Pelvis, with calices extending outward between the papillæ of the pyramids. 1'. Medullary rays, between which are the labyrinths 1''. 2'. Conducting tubules of the medulla. The line from 2'' runs to a point just below the corticomedullary line. A. Renal artery; at 5, 5 is shown its method of distribution. 3, 3. Transverse section of tubules. 4. Fat of renal pelvis. * Transversely coursing medullary rays. U. Ureter.

grams. The pyramid is the anatomic unit; the **Malpighian tuft,**

with its blood-vessels and the tube passing off as the proximal convoluted tube, the loop of Henle, the second or distal convoluted tube, and terminating in the conducting tube, constitutes the gland unit.

Histologically, the tubules are tracts of mucous membrane in which different portions of the tube are lined by epithelial cells having slightly different characteristics. The epithelium of the tuft is flat, with a tendency to cuboid outline; the epithelium of the convoluted tubes is more or less polyhedral. The cortex of the organ is made up of two histologic structures, which are most important from a pathologic standpoint; these are the labyrinth and medullary rays or pyramids of Ferrein. In a perfectly normal kidney these two elements can not be satisfactorily differentiated by the unaided eye; but with the occurrence of inflammation or of marked degenerative change the structures named are outlined with remarkable clearness. The thickness of the cortex varies considerably in health, and also depends on the size and general contour of the organ. A kidney may be short, with a thick cortex, or long, with a somewhat thinner cortex; there is, however, a more or less definite relation between the cortex and the medullary portion, which is sufficiently constant to be utilized for comparison. If a pyramid be selected which is cut through from apex to base, and a line be stretched from the apex of the pyramid to the capsule, it will be found that two-thirds of the line will rest upon the medullary portion of the pyramid and one-third upon the cortex; this rule is not absolute, but the sources of error are so slight that the rule is generally applicable, and, by applying this method of measurement, one can usually tell, at least approximately, whether the cortex is normal in thickness.

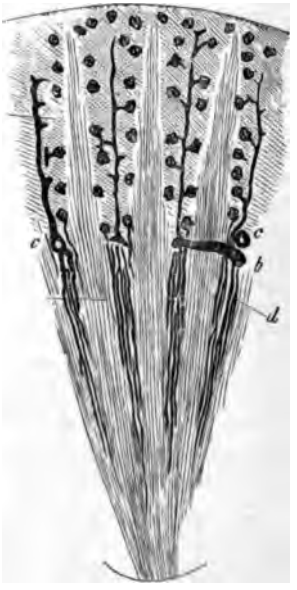


FIG. 281.—DIAGRAM OF BLOOD SUPPLY TO KIDNEY.—(*Rindfleisch.*)

b. Artery at the corticomedullary line, the same as 5 in figure 280. *c, c*. Blood-vessels passing upward to Malpighian tufts in the cortex. *d*. Blood-vessels passing downward into medulla. The diagram also shows the pyramids of the cortex, between which are the labyrinths containing the Malpighian tufts and convoluted tubules.

Malformations and Malpositions of the Kidney.—It is necessary to consider these conditions together, as malformed kidneys are not, as a rule, in their normal positions.

The **solitary kidney** represents a blending of the two organs and their development as a single mass. As a rule, the solitary kidney has a duplicated blood supply; it lies in the median line

FIG. 282.—SOLITARY KIDNEY. (Anterior view.)

A. Aorta. The small branch between *A* and the bifurcation of the aorta is the inferior mesenteric artery (?). *B*, *B*. Common iliacs. It will be observed that the two renal arteries appear to come off directly at the bifurcation of the aorta. *C*. Kidney. Just above the letter *C* is the ureter. Posteriorly, the organ is slightly lobulated. Absence of renal tissue between the two renal arteries would convert this mass practically into a horseshoe kidney.—(*Drawing from specimen in the Museum of the Jefferson Medical College.*)

or slightly to one side, and is very much nearer the pelvis than the normally placed organs; indeed, it may be on the brim or even in the pelvis. Commonly, there is but one ureter, although there may be two ureters or a single ureter dividing into two before it reaches the bladder, or two ureters uniting into one just before

the bladder is reached. The organ is likely to be floating, although it may be firmly attached.

Horseshoe Kidney.—Next to the solitary kidney, in degree of malformation, is the horseshoe kidney. In this condition the two kidneys may be one continuous mass, or they may be considerably separated, with a fibrous band uniting them. The horseshoe kidney lies with its convexity downward, and usually has two pelves and two ureters; very rarely, the horseshoe kidney may lie to one side of the median line. The blood-vessels

FIG. 283.—HORSESHOE KIDNEY. (Anterior aspect.)

A, *A*. Renal arteries. *B*, *B*. Ureters. In this particular case the two ureters pass downward to the bladder and enter separately. The end of the organ to the right shows considerable lobulation, such as is normal in fetal life, but usually absent in the fully formed kidney of the adult.

to such kidneys are usually abnormal, in that they arise from or join the larger blood-vessels lower than normally.

A **single kidney** is one more or less normal organ possessing the usual blood supply. It is due to arrest of development and absence of the opposite organ, and differs from the solitary kidney in that it does not, histologically or anatomically, although it may physiologically, represent the two organs. It is usually in the normal position, but, having enlarged, its increased weight

sometimes leads to loss of anchorage, and, consequently, to some form of acquired malposition.

Absence of the Kidney.—Rarely, both kidneys may be absent; absence of one kidney is not so uncommon. Usually, it is the left kidney that is absent; the remaining organ hypertrophies and performs the function of two kidneys. The kidneys are not uncommonly lobulated, retaining this characteristic of fetal life. Rarely, there may be a third kidney. The organ may be near one of the normally placed kidneys, but more commonly is

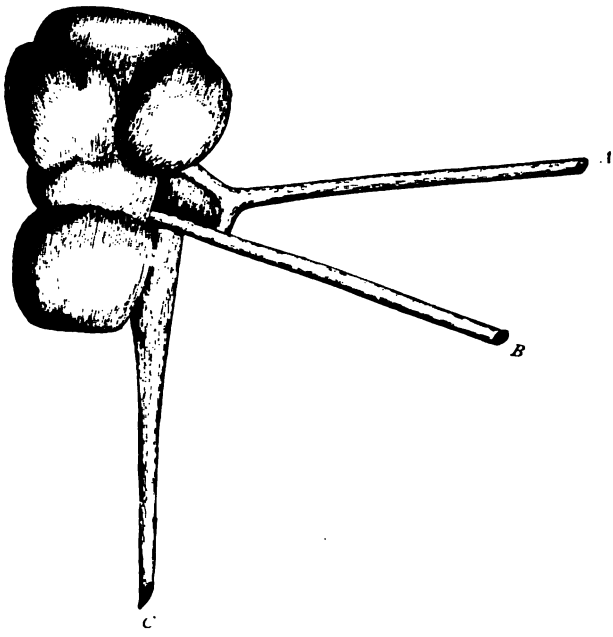


FIG. 284.—PERSISTENT FETAL KIDNEY DUE TO ANASTOMOSES BETWEEN THE RENAL ARTERY AND VEIN. (Natural size.)

A. Renal artery. *B*. Renal vein. *C*. Ureter. The persistence of fetal lobulation is well shown. It is occasionally just as marked in organs of a normal size.

situated lower in the abdominal cavity and possesses its own ureter and blood supply. The division of one kidney into two or more parts, receiving their blood supply from the same vessel and draining into the same ureter, does not really constitute an example of accessory or multiple organs.

Nephroptosis, or prolapse of the kidney, may be a part of a malformation, as already stated when considering solitary and horseshoe kidneys. In other cases it is distinctly an *acquired*

malposition. Over eighty per cent. of the misplaced kidneys are found in women. The morbid condition is most frequent during adult life, between twenty and forty, but is also seen in children and infants. The right kidney is the organ involved in over eighty per cent. of the cases. The displacement commonly follows pregnancy or other conditions that tend to bring about an abnormal flaccidity of the abdominal walls. It is frequently associated with morbid processes that increase the size and weight of the kidney. Nephroptosis may be associated with enteroptosis or prolapse of other viscera. It is said to be favored by absorption of the perirenal fat and abnormal length of the renal vessels. Trauma, in the form of blows and falls, may bring it about. Tight lacing is assumed to be a cause. The pressure upon the liver brought about by stays is transmitted to the kidney, which is thereby forced from its normal position.

The degree and, to a certain extent, the character of the mobility vary in different cases. The organ may be movable behind the peritoneum, constituting the so-called *movable kidney.* In other cases the kidney falls forward, bringing with it the peritoneum, thereby forming a pedicle composed of the blood-vessels, ureters, nerves, and peritoneum, constituting what is known as a *mesonephron.* In this condition the organ is movable within the abdominal cavity, and is called a *floating kidney.* Both the movable and floating organs not infrequently twist or kink the ureter, giving rise to obstruction and favoring the development of hydronephrosis. Less commonly, torsion may give rise to a temporary obstruction of the blood supply, and if the obstruction persist, gangrene of the organ may take place. The kidney may be displaced and caught by the adhesions, or in other ways incarcerated.

Malformations of the Ureter. — Sometimes the ureter is imperforate, or, the reverse, sacculated ; occasionally, one kidney may have several ureters.

Malformations of the Bladder, Urethra, etc.—Occasionally, the bladder is bifid ; sometimes there is a fissure of the abdominal and vesical walls, giving rise to **exstrophy, fissura,** or **inversio vesicæ ;** rarely, the bladder is fissured in its posterior wall, and thereby communicates with the pelvic cavity or with the vagina or rectum. The urethra may be imperforate, or the bladder and bowel may have a single opening ; the bladder may be absent. In a few instances the bladder has been found normally formed, but has protruded through a fissure in the abdominal wall—a condition known as *ectopia vesicæ.* Persistence of the urachus may be manifested by a conic

projection upward in the median line, the bladder reaching almost, if not quite, to the umbilicus. In other instances the atrophic allantois may remain as a tube-like projection above the bladder, ending at the umbilicus, or it may be closed at both ends. Later, accumulation of fluid in the tube may lead to the formation of a cyst, constituting what is known as a *cyst of the urachus*. The urethra may open on the dorsal aspect or on the inferior surface of the penis, giving rise to **epispadias** and to **hypospadias**, respectively. Occasionally, the urethra may have more than one external orifice; in rare instances the urethra opens behind the scrotum, giving rise to **hypospadias perineoscrotalis.**

Diseases of the Kidney.—For pathologic study of the urinary organs it will be necessary to assume that only a part of these structures has anything to do with the secretion of urine. The secreting structure is, of course, the kidney, and particularly that part of the organ lying superficially, and known as the cortex. A study of the relation of diseases of the kidney to the different parts of the organ will show that a number of conditions begin in, and are largely restricted to, the essential secreting tissue. To this group belong the various forms of Bright's disease and the acute degenerative processes, and constitute what are often called the *medical diseases of the kidney*. In another class of cases the lesions begin in the pelvis, ureter, or bladder, and extend by continuity along the course of the passage, eventually involving, in many cases, the secreting structure of the kidney. With this group of diseases are included the retention cysts of the kidney (hydronephrosis, pyonephrosis), suppurative lesions, and secondary suppurative processes in the urethra, prostate, bladder, ureter, and pelvis. By common consent these lesions are grouped under the term *surgical diseases of the urinary apparatus*. It will be observed that this division into the medical and surgical diseases is largely clinical, but has some foundation in that the morbid conditions that eventually manifest themselves are, to a certain extent at least, largely restricted to the structures just indicated.

Atrophy of the Kidney.—Aside from the arrest in development already referred to when considering malformation (and hypoplasia is really not an atrophy), but little is known of atrophic processes in the kidney. The small kidney resulting from chronic interstitial inflammation is sometimes referred to as an atrophied organ. (See Chronic Interstitial Nephritis, p. 623.)

Hypertrophy of the kidney occurs to a limited extent in both organs in individuals addicted to drinking large quantities

of fluid, and in whom the kidneys are thereby called upon for unusual activity. As a result of disease, of failure of development, or of removal of one organ, its fellow commonly shows more or less hypertrophy. The earlier in life the functional loss of one organ occurs, the more prompt, and, as a rule, the more complete, will be the compensatory hypertrophy of the remaining kidney. The power, however, of continued enlargement persists until late in life. During fetal life the destruction of one organ leads to enlargement of the remaining kidney until it approximates in volume two fully developed organs. At this time new tubules and new Malpighian tufts may be formed, but later in life, after the kidney has attained its normal dimensions, it is probable that the increase in size is due to a proportional increase in the size of the tubules, and is unassociated with the formation of new tubules or additional tufts.

Infiltrations of the Kidney.—Fatty and calcareous infiltrations are rare in the normal organ. Calcification is not infrequent in areas of past necrosis, such as those resulting from tuberculosis, infarction, etc. Occasionally, the kidney shows pigmentation as a result of the deposit of more or less altered hemoglobin. The color of the affected area or of the whole organ is brown, brownish-yellow, or mottled. Pigments so deposited may be rich in iron, as can be readily shown by the application of the usual tests. (See p. 236.) In jaundice more or less staining of the kidney tissue is always evident, and usually necrotic and desquamative changes give rise to casts that are intensely bile stained and recognizable in the urine. Aside from the concretions or true calculi occurring in the conducting portion of the urinary tract,—the pelvis, ureter, urethra, and bladder,—there is occasionally seen, in the kidney structure proper, within the tubules, and massed with more or less necrotic epithelium, deposits of uric acid and urates. The so-called *uratic infarcts* seen during the first two weeks of postnatal life are also examples of a deposition of a kind just described and occurring in the tubules of the pyramids. In diabetes a varying amount of glycogenic infiltration may be present in the renal epithelium, and, to a limited extent, in the Malpighian bodies. Lardaceous disease of the kidney will be considered with the renal inflammations.

Degenerations of the Kidney.—True fatty degeneration of the organ can probably be best considered with chronic parenchymatous nephritis, with which it is so constantly associated. A similar conversion of the renal epithelium into fat occurs in pernicious anemia. Parenchymatous degeneration (cloudy swelling)

is probably the most constant morbid condition to be recognized in the kidney. It may result from hyperemia, from congestion, or from the presence of various irritants, particularly those elaborated during the progress of infectious diseases, such as scarlet fever, diphtheria, pneumonia, erysipelas, etc. (See causes of acute Bright's disease, p. 617.)

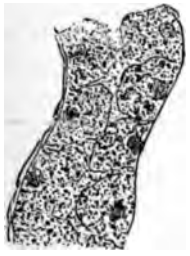


FIG. 285.—CLOUDY SWELLING OF THE EPITHELIUM LINING A KIDNEY TUBULE.—(*Flütterer.*)

Anatomically, the appearance of the organ is largely dependent upon the amount of vascular distention with which the lesion is associated. In the absence of hyperemia or congestion the kidney is pale, soft, and not infrequently pitting, as though it were edematous. The swelling is often inconspicuous, but can usually be shown to be present by the fact that, upon incision, the capsule retracts. In the absence of congestion or hyperemia the pale, cloudy surface contrasts strongly with the bright luster of the normal kidney. The histologic changes are those already described when considering cloudy swelling. (See p. 241.)

Hyperemia of the kidney is induced by exposure to cold, by the administration of irritant substances normally excreted through the kidney, and it also occurs in some febrile conditions, but not in all, and is present in the initial stage of acute nephritis. (See causes of acute Bright's disease.)

Morbid Anatomy.—The organ is somewhat larger than normal, soft, and, on section, drips blood. The cortex is very much darker than that of the normal organ, and is striated, while the medullary portion may be almost purplish. Microscopic examination usually shows distention of the entire vascular area, and, at points, rhexis; cloudy swelling is extremely likely to accompany the condition.

Congestion of the kidney arises as the result of impeded venous circulation, such as may occur in chronic heart or lung diseases, or, locally, from pressure on the renal veins by abdominal tumors, ascites, and a very much enlarged pregnant uterus. The most advanced form of congested kidney is the so-called **cyanotic kidney** of chronic heart disease.

Morbid Anatomy.—The organ is usually large and swollen, and may drip blood on section. The tissue is firmer than normal, and resists cutting and tearing, owing to the increase in connective tissue; unlike interstitial nephritis, the capsule usually strips more easily than normal; the cortex is of a deep-red color and striated,

and the pyramids are purplish. Microscopically, the epithelium is cloudy or granular, and at points almost fatty; there is some increase in the interstitial connective tissue, as shown by a small lymphoid cell accumulation between the tubes, and also an increase in the fibrous tissue—an evidence of past exudation. The amount of fibrous tissue may be sufficient to lead to a slight reduction in the size of the organ; when the kidney is perceptibly smaller than normal, it is reasonable to assume that an associated interstitial inflammation is present. The blood-vessels are intensely engorged, but there is less likely to be evidence of rhexis than in the condition of hyperemia.

Inflammation of the kidney may be acute or chronic. Its manifestations may be largely restricted to the connective tissue of the organ, in which case it is said to be an *interstitial inflammation.* In other cases the epithelium of the tubules and tufts suffers most, to a certain extent justifying the term *parenchymatous nephritis.* There can be, however, no inflammation of one of these structures without involvement of the other. Histologically and physiologically, the two structures are inseparable. In certain classes of cases, however, the inflammatory process seems to explode itself, as it were, upon one or the other elements, the remaining structure being but incidentally involved. This fact, taken with the well-known and recognized clinical distinctions, seems to justify the division of renal inflammations into two groups, as previously indicated; each of these will be further considered as occurring in two forms—acute and chronic.

Acute parenchymatous nephritis, also known as *acute Bright's disease, acute diffuse nephritis, acute nephritis, acute tubular* or *tubal nephritis, acute catarrhal nephritis,* and *fibrinous nephritis,* arises as the result of overwork or of the application of irritants to the kidney, or of both causes acting together.

The increased work may be due to cold or exposure, or to suppression of cutaneous functions, as in burns, scalds, and extensive skin lesions from other causes. Irritants may reach the kidney as a result of the administration of turpentine, cantharides, potassium chlorate, carbolic acid, and, occasionally, cubebs and copaiba. Acute nephritis accompanying the infectious fevers, particularly scarlet fever, and the same lesion arising in the course of such diseases as typhoid fever, diphtheria, and septicemia and other blood mycoses, is probably the result of an attempt on the part of the organism to excrete, through the kidney, some substance that is an irritant to the already overworked organ. The same is true of the acute nephritis that at times accompanies gestation, although it is held by some authorities that pressure upon the

veins from the kidney by the enlarged uterus is partly responsible for the lesion.

The toxic agents inducing this form of kidney inflammation are, no doubt, of many kinds; they may, however, be divided into three groups:

1. Those arising as products of tissue metabolism, exclusive of the influence of bacteria.

2. Bacterial poisons.

3. Toxic agents introduced from without—in other words, poisons, in the ordinary acceptation of the term.

Morbid Anatomy.—In the earlier stages of some cases of acute nephritis there may be but little alteration in the macroscopic appearances. As a rule, early in the inflammation the organs are intensely swollen, the capsule is tense, and, on incision, retracting, thus showing the abnormal tension of the inclosed kidney structure; the surface may drip blood; it is dark and striated, the striæ becoming evident as a result of the intensely engorged condition of the labyrinth, the area composed of convoluted tubules and Malpighian tufts. The capsule strips off with unusual readiness. As the disease progresses the incised surface appears more yellow and less hyperemic; striation will still be visible, but is altered in that the indistinct red lines of the cortex are replaced by lines of yellow striation, due to the granular and fatty change beginning in the convoluted tubules and tufts; swelling is usually evident, but now it is not so much the enormous increase in blood as it is the swelling of the epithelium in the tubules and tufts.

Histology.—In the earlier stage, first described, there will be found an intense engorgement of the vascular loops within the tufts, which may be enormously distended, and hemorrhage will probably have occurred within the tuft capsule. The epithelium will be found intensely swollen and somewhat granular; the tubules may contain blood-casts. Blood-casts will also be found in the urine. A little later the capillary system fails to show such engorgement as that just described; the Malpighian tuft will be hyaline, and the epithelial lining swollen, desquamating, possibly granular, and, in rare instances, fatty; there is likely to be some proliferation of the connective-tissue cells between the tubes, and leukocytic infiltration of the interstitial structures—the mesoblastic elements—around the tufts and between the tubules. Further down in the tubules the epithelium will be cloudy, or, it may be, finely granular or hyaline, and may show fatty, associated with granular, change. The nuclei of the epithelial cells are indistinct, granular, or unrecognizable. Between

FIG. 1.

Kidney, Chronic Interstitial Nephritis. See p. 625. (*Atlas of Pathology*, Sydenham Society.)

FIG. 2.

Part of Kidney, Subacute Parenchymatous Nephritis. From girl 6½ years old. Scarlet fever; death on the forty-seventh day. More advanced degenerative change than in Fig. 4. (*Atlas of Pathology*, Sydenham Society.)

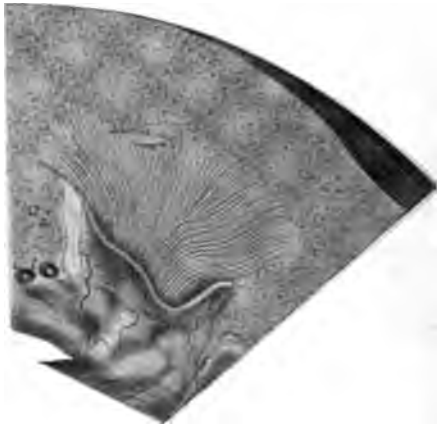
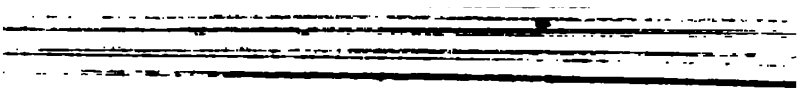


FIG. 3.

Kidney, Chronic Parenchymatous Nephritis. (*Atlas of Pathology*, Sydenham Society.)

FIG. 4.

Part of Kidney, Acute Parenchymatous Nephritis. From boy 9 years old. Scarlet fever; death on the twenty-second day of the disease. The initial stage of engorgement is no longer present. (*Atlas of Pathology*, Sydenham Society.)



the tubules, in ordinary cases, very little change occurs; there may be some swelling and a few leukocytes scattered through the interstitial tissue of the cortex. In graver or more protracted cases more or less of the interstitial connective tissue shows the result of proliferation, and contains a varying number of lymphoid and hyaline cells.

Changes in the Urine That Accompany the Changes in the Kidney.—In the earlier stage, with marked hyperemia and hemorrhage into the tufts, there is likely to be an enormous reduction in the amount of urine; actual suppression may be attained. The urine, when voided or drawn, is high colored, smoky, or even darker in hue, and of high specific gravity. The sediment contains an abundance of desquamated epithelium, blood, and casts. In the earlier stages the casts are made up of blood, which greatly diminishes in amount as the hyperemia is relieved; following the blood-casts, the epithelial cells form the casts, and as these undergo the various changes from cloudiness to advanced fatty degeneration, the condition of the kidney may be inferred by the predominating change observed in the casts. The various forms of casts are illustrated in the chapter on Microscopic Examination of Urine. (See pp. 124 and 125.)

The amount of albumin present in the beginning may be so great that a small test-tube containing the urine, if immersed in boiling water, may have its contents fully solidified. As recovery proceeds the epithelium seen in the casts improves, and eventually disappears; a few hyaline casts continue for a short time, but gradually no more can be found; the albumin slowly diminishes and eventually disappears, the reduction in urea is fully made up, and the kidney resumes its normal functions. When the disease is progressing into the chronic form, epithelial cells, as seen in the casts, do not return to anything like their normal condition, but remain more or less granular and sometimes fatty; the amount of urine remains diminished, urea excretion does not rise to the normal, and albumin persists in a varying quantity.

In acute nephritis cardiovascular changes do not occur; anemia is a marked symptom; edema, anasarca, and effusion into the serous cavities accompany the more marked cases. Evidences of systemic poisoning, due to the retention of the products of tissue metabolism, may be manifest clinically, although they are rarely, if ever, demonstrable postmortem.

Termination.—This is largely dependent upon the early withdrawal of the cause; if repair began before the production of any new tissue in the interstitial structure, the organ may be completely restored; if a large quantity of new connective tissue has

formed, there must be more or less permanent injury; greatly impaired organs, or cases in which the cause is long applied, may terminate in chronic parenchymatous change.

Chronic Parenchymatous Nephritis, also known as *Chronic Diffuse Nephritis, Chronic Desquamative Nephritis, Chronic Tubal Nephritis, Large White Kidney,* etc.—This condition may arise (1) as a sequence of the acute inflammation already described; (2) occasionally it comes on insidiously, without any distinctly antecedent inflammatory disorder. In the latter group of cases are included those that are believed to follow overwork of the kidney, as in beer drinkers and consumers of large quantities of alcohol; chronic suppuration and chronic infections, such as tuberculosis and syphilis, are assumed to be, at times, etiologic factors; the disease occasionally follows acute febrile processes, and has been observed after prolonged malarial infection; it may accompany, or follow, or be followed by, amyloid disease of the kidney. Chronic parenchymatous nephritis is a disease of young adults and, occasionally, of children.

Morbid Anatomy.—Two forms of chronic parenchymatous nephritis are recognized: one in which the kidney is large and one in which the organ is small. The former is known as the *large white kidney* or *large fatty kidney*, and the latter as the *small white kidney* or the *pale granular kidney.*

In the large white kidney the organ is very much enlarged, pale, white, or yellowish-white, and the capsule is thin and may appear edematous; scattered at irregular intervals over the surface will be seen stellate veins, usually intensely distended. On section, the swelling is manifested by the retraction of the capsule as soon as it is incised; the cortex is enormously swollen, and may be as thick as the medulla. It bulges forward and stands out prominently; the pyramid appears slightly sunken; the cut surface is pale, yellowish-white, and at points may be opaque; in contrast to the yellowish-white color of the cortex, the pyramids are dark.

Histology.—The epithelium of the tubules is granular, fatty, and desquamating; many of the convoluted tubes will be found distended with hyaline, fatty, or granular casts. The epithelium of the tufts is desquamating, and shows the changes already described as present in the tubules. The capillaries of the tufts are frequently hyaline; the capsule of the tufts and the basement membrane of the tubules are both likely to be slightly increased in thickness, and the intertubular connective tissue may be more abundant than normal, but this increase is usually slight; there is, however, marked swelling.

In the *large white kidney* there may be a tendency toward the development of hemorrhage in the cortex, and these areas may be found postmortem as brownish or yellowish-brown spots. The hemorrhage is probably due to increased vascular tension without corresponding increase in the thickness of the capillary

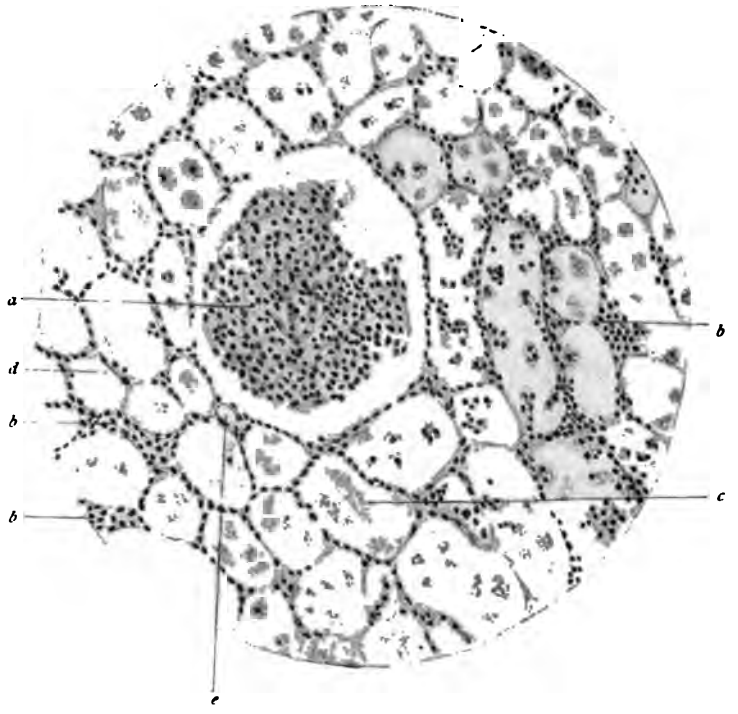


FIG. 280.—CHRONIC PARENCHYMATOUS NEPHRITIS. (1/6-inch objective, 1-inch ocular, slightly reduced.)

Tissue hardened in corrosive sublimate, infiltrated with paraffin, and stained with hematoxylin and eosin. *a*. Malpighian tuft, containing an unusual number of nuclei. *b*, *b*, *b*. Points at which there is some slight increase in the interstitial tissue. This is not, however, at any point marked. *c*. Tubule containing granular, degenerating, epithelial cells, which have coalesced. In many tubules the fragmented and desquamated epithelial cells in all stages of granular change are to be seen. In no tubule are the epithelial cells normal or normally arranged. *d*. Tubule from which all the epithelium has desquamated and been discharged. *e*. Blood-vessel. (Kidney from a case of tubal nephritis that terminated in death from eclampsia at the end of eleven weeks after the appearance of the first symptoms.)

walls; or the fatty changes in the perivascular tissue may so weaken that structure as to withdraw the normal support to the blood-vessel, thereby favoring rhexis. The condition is sometimes called *chronic hemorrhagic parenchymatous nephritis*.

The *small white kidney* differs from the preceding in that its

surface is granular, its capsule more adherent, its cortex less swollen; indeed, the latter may be thinner than that of the normal organ; the kidney is firm, and cuts with more resistance than the normal. Histologically, the same tubular and tuft changes as those already described in the large white kidney will be found present; there is, however, a marked increase in the connective tissue, more marked in some places than in others; many of the tufts will be found atrophied, and many of the tubules compressed or occluded by the contraction of the newly developed connective tissue.

If one looks merely at the pathologic picture that this type represents, he is led to view the condition as one of chronic tubular inflammation, with superadded interstitial change. As will be seen later, there are many of the elements present that are to be noticed in the chronic interstitial nephritis, and, as already described, many of the changes constantly associated with parenchymatous nephritis, and there is no pathologic reason, either etiologic or anatomic, for believing that it is impossible for the two forms of nephritis to intermingle. At present this question can not be definitely settled, so that writers variously classify the small white kidney, some holding that it is produced in a way entirely distinct from the chronic parenchymatous or the chronic interstitial, others maintaining that it is but a form of the chronic parenchymatous or a tubular lesion ingrafted on an interstitial nephritis, or a parenchymatous nephritis that has persisted sufficiently long to have developed fibroid changes in the intertubular connective tissue. When the kidney is considered as a mucous membrane, the resemblance between the changes seen in the submucosa after protracted inflammations of the mucous membranes and the interstitial changes observed in the kidney subsequent to a prolonged inflammatory lesion of the tubules become quite evident.

Changes in the Urine Accompanying Chronic Parenchymatous Nephritis.—The urine is diminished in quantity, of high specific gravity, usually highly colored, albuminous to a marked degree, and commonly contains an abundant sediment, in which will be found all forms of casts that may arise from any structural lesion of the epithelium lining the tubules. Granular and fatty casts, indicating the changes in the epithelium; hyaline and epithelial casts containing leukocytes; and, occasionally, red blood-corpuscles, although these are rare, indicate the inflammatory lesion that is accompanying the process of degeneration. There is a reduction in the excretion of the products of metabolism.

When the process is long continued and it is probable that the large white kidney is being converted into the small white kidney, or that the latter is arising independently, the urine will be more abundant than from the large white kidney and the albumin will be less abundant. Commonly, the small white kidney seems more fully to perform its functions than the large white organ.

The disease may be accompanied by alterations in the vascular system resembling those of chronic interstitial nephritis; although rare, retinal lesions are not unknown; when the kidney shows a tendency toward contraction (small white kidney), the vascular and retinal changes are more commonly present. Anemia and edema are likely to accompany all forms of parenchymatous nephritis, and dropsical accumulations in the serous cavities and subcutaneous connective tissues are of frequent, one might almost say constant, occurrence.

Acute Interstitial Nephritis.—The changes seen in the connective tissue of the kidney in acute parenchymatous nephritis have already been mentioned, and to a certain extent merit the appellation *acute diffuse nephritis.* It has been suggested that the so-called chronic interstitial nephritis is dependent upon a succession of acute interstitial changes. There seems, however, no sufficient reason for regarding this process as other than essentially chronic. The typical acute interstitial inflammation is suppurative in character, and may depend upon the deposit of infected emboli, in which case there occur abscesses varying in size and possessing the usual characteristics of embolic suppuration. In other cases the acute interstitial change is dependent upon an ascending infection, the pyogenic bacteria extending from the contiguous structures, and therefore involving the medullary and cortical portions of the kidney secondarily to the pelvis. The condition is most frequently observed in connection with the suppurative processes secondary to enlargement of the prostate and septic inflammations of the bladder. To this condition has been applied the term **pyelonephritis.** The lines of suppuration between, and involving, the conducting tubules of the pyramids appear as grayish striæ in the medullary portion, sometimes extending into the cortex.

Chronic interstitial nephritis, also known as *contracting* or *contracted kidney, granular kidney, fibroid kidney, cirrhotic kidney, gouty kidney, renal sclerosis,* and, occasionally, as *hobnail kidney,* is a chronic interstitial inflammation of the kidney analogous to interstitial inflammation of other granular viscera: *e. g.*, interstitial inflammation of the liver and interstitial inflammation of the pancreas.

Etiology.—That the large white kidney, already described, ever becomes converted into the kidney at present under consideration seems very doubtful; that the small white kidney might eventually terminate in a fibroid organ is possible; but in a large majority of cases, if not in all, this disease is primary, and is not preceded by any of the lesions already considered. There may be no apparent cause; heredity is a possible influence; continual

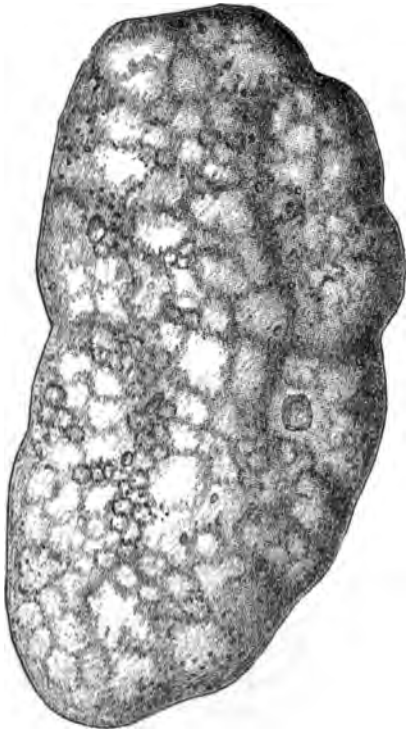


FIG. 287.—KIDNEY SHOWING CHRONIC INTERSTITIAL NEPHRITIS. (Natural size.)
The surface is granular and slightly lobulated. The process depicted in this organ is not so advanced as that shown in figure 288.

demand upon the kidney for the excretion of irritant materials is probably a most constant factor; examples of this are to be noted in alcoholics, in sufferers from gout and lithemia, in chronic lead-poisoning, and in individuals who subsist upon a diet composed largely of substances whose metabolism terminates in uric acid. Persistent overwork of the kidney may be a factor. As to age, the phenomena of the disease usually manifest themselves only

in advanced life—forty years or later; the disease is rare in younger individuals; it is probable, however, that the lesions begin much earlier than the clinical data would seem to indicate.

Morbid Anatomy.—The kidneys are diminished in size, and may weigh no more than from 100 to 125 grams; both organs may not be equally involved. The surface of the kidney is uneven, irregular, and indurated, and the capsule can not be cleared of the perinephritic fat so easily as the normal kidney. The organ is very firm, is hard and slightly elastic, and resists cutting to such a degree that it may creak under the knife; the color varies —it is usually red or reddish, or, when the organ is markedly

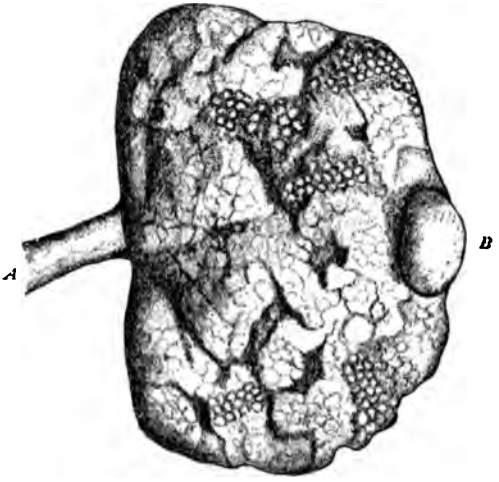


FIG. 288.—KIDNEY SHOWING ADVANCED CHRONIC INTERSTITIAL NEPHRITIS. (Natural size.)

A. Ureter. *B*. Small cyst just under capsule. The irregularly lobulated, coarsely and finely granular surface is well shown.

anemic, may be somewhat pale; it never has the yellowish, fatty appearance described in the chronic parenchymatous inflammation. The capsule usually strips off with great difficulty, and it is firmly adherent to the underlying tissue, part of which may pull off with the capsule. In some cases the newly formed fibrous tissue is not immediately subcapsular, and therefore does not tie the capsule closely to the organ. The capsule is markedly thickened, and immediately under it may be found small cysts varying in size from that of a pinhead to that of the end of one's thumb, rarely larger; these cysts are near the surface, and may be ruptured in removing the capsule. The cyst contents are

usually clear or slightly straw-colored. In very rare cases there may be hemorrhage into or around the cyst.

In comparing the cortex with the medullary portion the observer will be immediately struck with the contrast between the condition now being described and the cortex in chronic parenchymatous nephritis. The cortex is irregularly thin, and there may be pyramids in which, macroscopically, the cortex can not be demonstrated. Occasionally there will be a pyramid possessing its normal quota of cortex, thus illustrating the patchy character of the lesion; as a rule, however, the cortex, covering all the pyramids, is more or less contracted. The pyramids are but slightly wasted. There is usually considerable fat in the pelvis, which is less capacious than normal. That the morbid anatomy of this condition varies could not be better shown than in figures 287 and 288, and plate IV, figure 1.

Morbid Histology.—Sections show that the lesion is patchy and not universally distributed throughout the cortex; here and there will be seen small areas in which the changes are most marked; at other points there will be areas in which very little change is discernible. The fibrous tissue will be most markedly increased in the labyrinth, less so in the pyramid of Ferrein, and very much less in the medullary portion. Between the tubules, in the interstitial connective tissue of the organ, will be found new cell-growth in various stages of development—the more recent cellular accumulations, composed of lymphoid cells. Where organization is in process these round cells will be seen gradually forming into spindle-shaped elements, through the activity of which fibrous tissue is eventually produced. The newly formed cicatricial tissue contracts, and presses upon the blood-vessels, Malpighian tufts, and tubules, thereby lessening the blood supply, the nutrition, and the functional activity of these structures. The capsules of the glomeruli are thickened by the progressive fibrosis, and the contraction of the newly formed fibrous tissue leads to destruction of the capillary tuft, preceded or followed by hyaline change. Glomeruli whose vascular supply is still normal have thickened capsules; the thickening of the capsule is continuous with the thickened basement membrane of the tubule. The epithelium of the tubules shows various changes dependent upon the influence of the interstitial deposit within any given area. The large, swollen, granular, fatty, tortuous tubules of parenchymatous nephritis are not found; instead, the tubules are diminished in size in those areas in which the new tissue is most rapidly organizing; the gradual contraction may occlude tubules and give rise to dilatation or dis-

tention above the point of obstruction, thereby accounting for the cysts already described. Where the tubule is being influenced by the contraction, the epithelium is atrophied and finely granular, and the cells are greatly diminished in size; where the fluids are retained within the tubule by obstruction below, the epithelium is flattened, hyaline, granular, or even fatty; occasionally, tube-casts may be seen *in situ;* if the epithelium

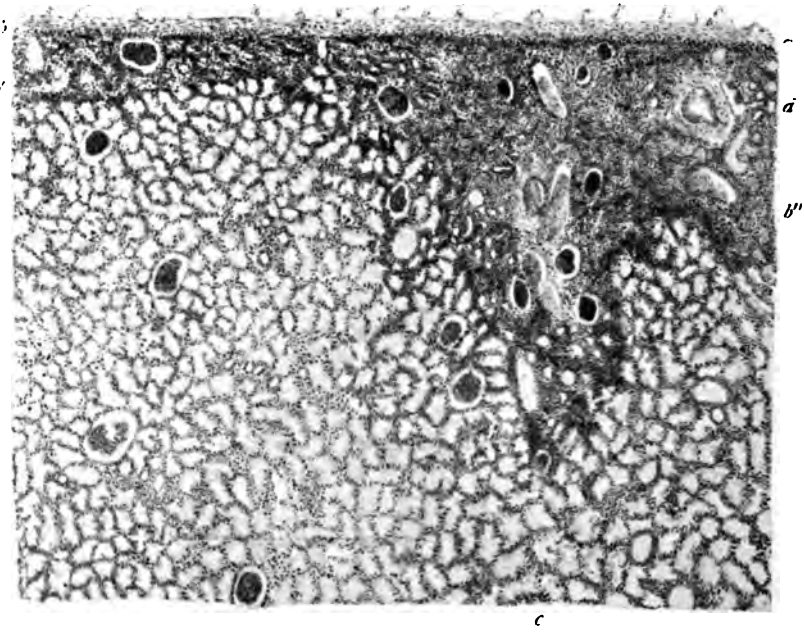


FIG. 289.—KIDNEY, CHRONIC INTERSTITIAL NEPHRITIS. (¼-inch objective, 1-inch ocular, slightly reduced.)

Specimen fixed in corrosive sublimate, infiltrated with paraffin, and stained with hematoxylin and eosin. *a*. Slightly thickened capsule. *b*, *b'*, *b''* and *a* bound the area of most marked interstitial change, although an increase of the interstitial tissue is evident between *b''* and *c*. About one centimeter to the left of *d* is seen a beginning cyst. In the area of most marked interstitial change are a number of degenerating Malpighian tufts, while but a few of the tubules are recognizable. The new tissue is not yet fully developed, but at points, as around the cyst *d*, shows partial conversion into fibrous tissue.

or interstitial tissue be pigmented, it is probably the result of previous hemorrhage. The blood-vessels of the kidney show the same changes as are observed in similar structures elsewhere.

The *urine* is increased in quantity, light in color, and may be almost colorless; its specific gravity is rarely over 1012 or 1015, and may fall as low as 1005; albumin is present in varying amounts; sometimes the albumin may be scanty and may escape

detection, or, for short periods, rarely long, it may be entirely absent; as a rule, there is no sediment, and the dissolved solid constituents—salts and urea—are diminished. The casts found are usually hyaline; they are not abundant and not constantly present; during acute exacerbations in the inflammatory processes the phenomena of nephritic hyperemia may be observed.

Changes in the Vascular System.—The heart shows marked hypertrophy or dilatation, and there is a general arteriocapillary fibrosis. (See p. 518.)

Inflammation of the serous membranes is a frequent complication; retinal lesions are not uncommon; edema, anasarca, and accumulations of fluid in the serous cavities, such as occur in chronic parenchymatous nephritis, are usually absent.

Amyloid disease of the kidney arises in connection with general amyloid disease. (See p. 228.) The process is frequently associated with a more or less fully developed chronic parenchymatous nephritis, of the kind already described.

Morbid Anatomy.—In the vast majority of cases the kidney is much increased in size; in a very few instances it may not be larger than the normal. The veins of the capsule are dilated, the surface is smooth, and the organ is firm, but not fibroid. The tissue cuts with more resistance than in uncomplicated chronic parenchymatous nephritis; the cortex is much thickened, is glistening or hyaline, is slightly swollen, and the Malpighian tufts, in which the lesion is most manifest, may be readily picked out. The pale, hyaline, or semitranslucent cortex contrasts with the deep-red or, at times, almost purplish medullary portion; the usual tests for lardacein will demonstrate the character of the process.

The urine is usually abundant, pale, clear, and of a low specific gravity; hyaline, granular, or fatty casts are frequently present, and, occasionally,—not constantly, as commonly believed,—waxy casts that may give the amyloid reaction. The changes in other organs and tissues are dependent upon the general amyloid infiltration or upon the character of the accompanying renal lesion: *e. g.*, if there be parenchymatous nephritis, dropsy, edema, etc., may be present; if attended by interstitial nephritis, which is rare, the vascular and other phenomena of that condition may be manifest.

Pyelitis is an inflammation of the pelvis of the kidney; **pyelonephritis** is inflammation of the pelvis and kidney, the inflammation of the kidney being secondary to that of the pelvis. (See Acute Interstitial Nephritis, p. 623.) These inflammations may be catarrhal, pseudomembranous, gangrenous, suppurative, or hem-

orrhagic; they usually occur in connection with infectious diseases, or may be due to the irritation of drugs excreted by the kidney, such as cantharides, turpentine, etc. In pyemic processes the inflammations are likely to be suppurative, or suppurative processes may invade the pelvis by extension from the bladder.

Stone in the kidney or stone in the ureter is constantly attended by some of the forms of mucous membrane inflammation. The same is true of stone in the bladder. Inflammations in these structures may be attended by ulceration, by gangrenous processes, and marked thickening of the submucosa. As a result of prolonged ureteritis, thickening, and induration, the ureter may be constricted,—strictured,—the obstruction thereby produced leading in time to hydronephrosis. Occasionally, the infection may extend through the mucosa and invade the perinephritic tissues, giving rise to a condition known as **perinephritic abscess.** Injuries, such as falls and bruises, are said to predispose to abscess formation in the fat around the kidney. Perinephritic abscess may, of course, arise from any pyogenic infection which reaches the fat in which the kidney lies; the bacteria may invade this structure from the pelvis or body of the kidney or by way of the blood. As already stated, the foregoing forms of inflammation in the conducting apparatus are classed with what are known as the surgical diseases of the kidney.

Cystitis.—*Inflammation of the bladder* may be catarrhal, pseudomembranous, gangrenous, hemorrhagic, or suppurative. Pseudomembranous processes are by far the most rare, the catarrhal the most frequent; suppurative inflammation of the bladder is not uncommon; very rarely the inflammatory process in the bladder may lead to inflammatory conditions of the connective tissue surrounding the bladder—**pericystitis.** Occasionally, abscess formation occurs in the bladder-wall; such purulent accumulations are usually small and multiple, and may rupture into the bladder or externally.

Besides the suppurative and gonorrheal infections of the bladder, numerous bacteria may gain access to the organ from dirty catheters, etc., and give rise to putrefaction of the contained urine, with absorption of bacterial products and general systemic septic phenomena. On the other hand, bacteria in the blood may be excreted by the kidney, and in that way give rise to infection of the conducting apparatus. Such infections are intensified by obstructive diseases that prevent the bladder from emptying, such as strictures of the urethra, tumors, and diseases of the prostate; obstructive lesions also lead to hypertrophy of the muscular coat of the bladder. The bladder may be dilated as a result of obstruction

detection, or, for short periods, rarely long, it may be entirely absent; as a rule, there is no sediment, and the dissolved solid constituents—salts and urea—are diminished. The casts found are usually hyaline; they are not abundant and not constantly present; during acute exacerbations in the inflammatory processes the phenomena of nephritic hyperemia may be observed.

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Besides the suppurative and gonorrheal infections of the bladder, numerous bacteria may gain access to the organ from dirty catheters, etc., and give rise to putrefaction of the contained urine, with absorption of bacterial products and general systemic septic phenomena. On the other hand, bacteria in the blood may be excreted by the kidney, and in that way give rise to infection of the conducting apparatus. Such infections are intensified by obstructive diseases that prevent the bladder from emptying, such as strictures of the urethra, tumors, and diseases of the prostate; obstructive lesions also lead to hypertrophy of the muscular coat of the bladder. The bladder may be dilated as a result of obstruction

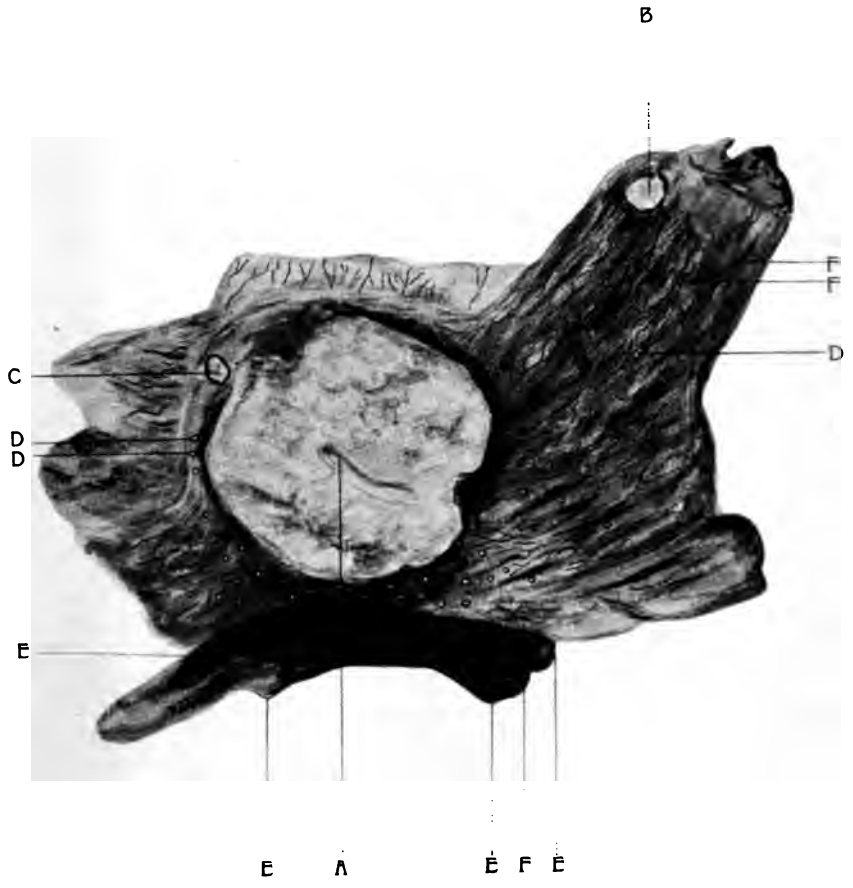
or of paralysis of its muscular wall; *rupture* of the bladder may follow injury, overdistention, perforation by instrument or disease, ulcer, or necrosis. The bladder may communicate by abnormal routes with the adjacent cavities, or externally; such pathologic passages are known as *urinary fistulas.*

Tuberculosis of the urinary organs may occur as an acute miliary process involving the kidney, and, it may be, all the urinary and genital organs and constituting a part of a general miliary tuberculosis. In these cases the tubercles are commonly most conspicuous in the secreting structures of the kidney, where they possess the macroscopic and microscopic characters commonly observed in miliary tubercles. In the so-called *chronic* or *caseous type* of tuberculosis involving the urinary organs two courses of extension are to be observed: (1) In this form the lesion may begin in the kidney or pelvis, from which it invades the ureter, bladder, urethra, etc. This constitutes the so-called *descending form of tuberculosis of the urinary organs.* (2) In other cases the initial lesion appears in the bladder, prostate, and seminal vesicles, and, far less frequently, in the testis and urethra.

Beginning in the kidney structure, it is probable that the infection occurs through the blood. There is usually the development of small tubercles, which coalesce and form caseous areas, which at first may be strictly localized in some part of the organ; later, by peripheral invasion, one or more pyramids may be involved, and eventually the whole organ may be converted into a series of irregularly outlined caseous collections (*scrofulous kidney*). From the kidney extension usually occurs, sooner or later, to the pelvis, and eventually to the ureter and bladder.

In other cases an ascending lesion, beginning as previously indicated, invades the ureter and pelvis and eventually the kidney. Frequently the ureter is obstructed, and accumulation of the inflammatory and necrotic materials gives rise to more or less distention of the pelvis. Later, the renal structure is involved, and eventually caseous collections are formed in the medullary and cortical portions of the organ. (See Fig. 290.) The disease may be restricted to one kidney, although it is commonly present in both; rarely, however, do both kidneys show the same degree of involvement.

The morbid anatomy of **tuberculosis of the bladder** is largely dependent upon the extent of the infection and upon the method by which the organ is invaded. The lesion may be circumscribed or diffuse, the latter constituting a miliary tuberculosis of the vesical mucosa. In the circumscribed or focal type of the lesion the ulcerative process is usually secondary to a primary lesion in



TUBERCULOSIS OF THE BLADDER

Drawing made from fresh specimen
One-half natural size
DRAWN BY MISS E. G. HARDING

LABORATORIES OF THE JEFFERSON MEDICAL COLLEGE HOSPITAL

A.—Centre of large ulcer. At the end of the line is a distinct furrow, to which was attached a recent slough.

B.—Similar ulcer, but more recent. This is the ulcer from which most of the sections were made, including the one shown in the microscopic drawing accompanying this article.

C.—More recent ulcer almost ready to become confluent with the large ulcer.

D.D.D.—Miliary tubercles. These at first glance resembled ulcers, but close inspection showed that they had not as yet broken down. Many of these are seen, particularly at the base of the bladder.

E.E.E.E.—The point from which was excised the trigone prostate and urethra.

F.F.F.—Points showing the patchy inflammation of the mucosa, which accompanies tuberculosis of the bladder.

the kidney or ureter, or in the prostate or seminal vesicle. Usually, the ulcer is in or near the trigone, and commonly involves the ureteral orifices. The ulcers are usually round, although they may be irregular. The floor is shaggy and of a dirty yellowish color, with uneven surfaces. As a rule, the necrotic process does not invade the muscle, although Senn observes that the vesical wall may be perforated. The edges of the ulcer are

FIG. 290.—TUBERCULOUS PYELONEPHRITIS; CHRONIC ASCENDING TUBERCULOSIS OF THE KIDNEY.

Specimen shows cavities in medullary and cortical portions of the organ, due to the extension of tuberculosis from the pelvis.

usually elevated and slightly undermined. They are indurated and extremely vascular, and not infrequently are sources of hemorrhage. The ulcers may be single or multiple, and do not commonly grow larger than one or two centimeters in diameter. In the specimen from which the accompanying illustrations (plates V and VI) were taken the diameter attained was seven centimeters. Not infrequently the adjacent mucosa, and sometimes the entire

vesical lining, may contain miliary tubercles. The bladder-wall is usually thickened, the thickening being partly due to an increase in the muscle and to an interstitial inflammation associated with the production of fibrous tissue. The tubercles in the submucosa are superficially placed, and possess the usual characteristics of miliary tubercles, except that, in the instances coming under the author's observation, they were not so indurated nor palpable as is usual. (See Plates V and VI.)

Syphilis of the urinary organs, aside from the external initial lesion, occurs as gummata of the kidney; these may lead to

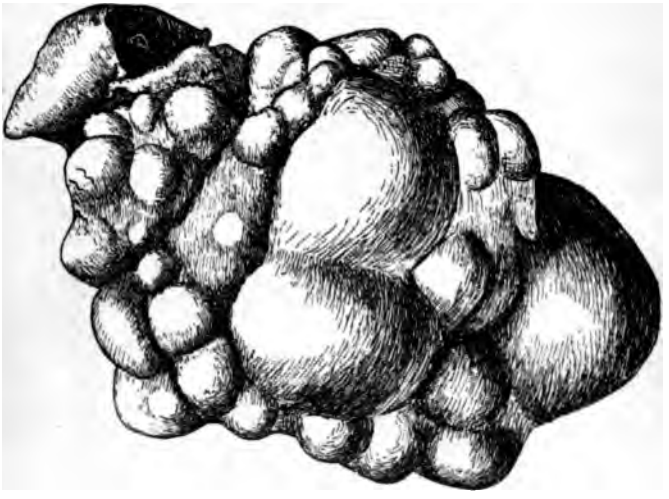


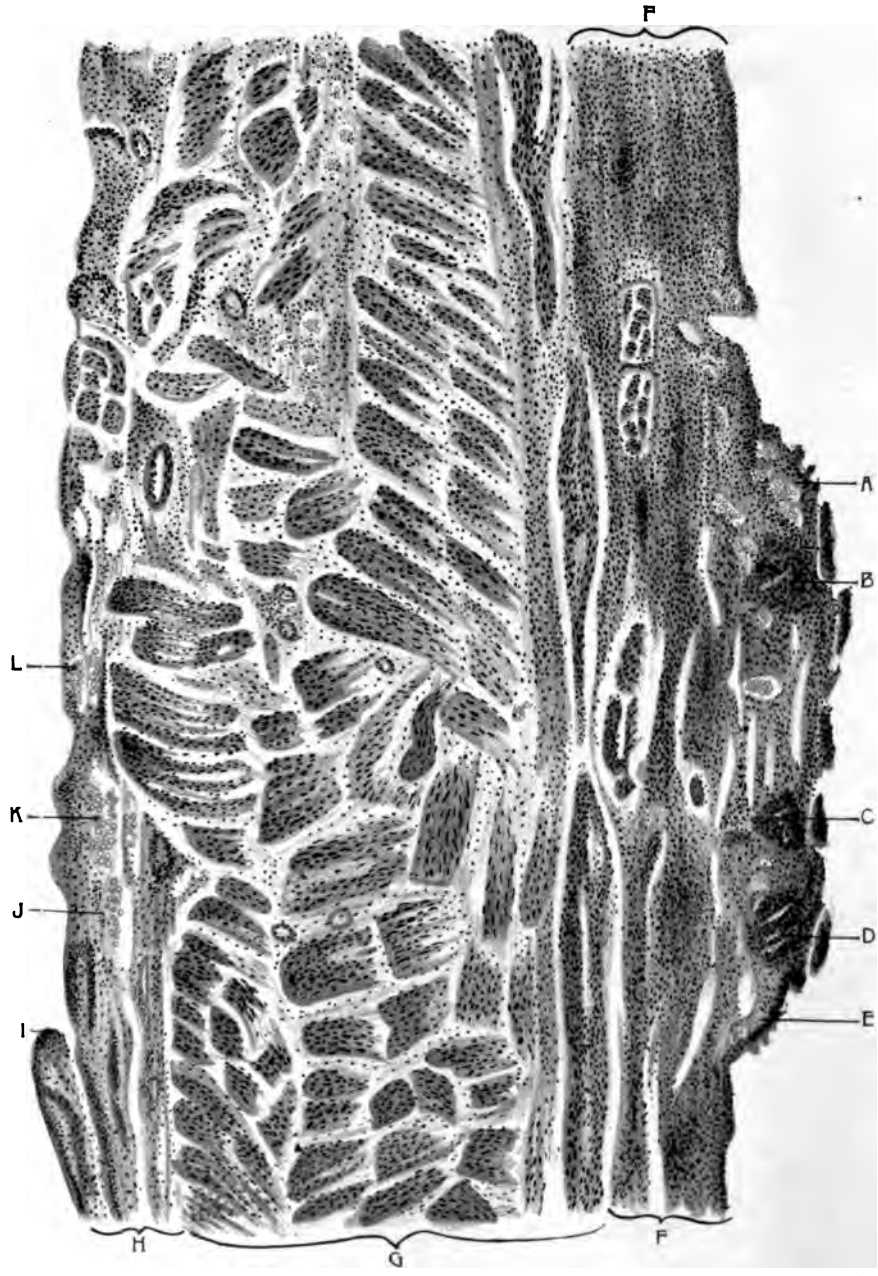
FIG. 291.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. (Natural size.) (From specimen presented by Dr. E. E. Graham. Original article in "Archives of Pediatrics," October, 1899.)

Figures 292, 293, 294, and 295 are from the same specimen.

scars in the kidney or may remain more or less hyaline and caseous.

Leprosy rarely invades the urinary organs, although leprous disease of the kidney has been observed.

Tumors.—*Adenomata* occur in the kidney structure. *Papillomata* have been observed in the pelvis. *Carcinomata* are rare, and occur as encephaloid and, rarely, as hard cancers. Of the adult connective-tissue tumors, *fibromata* are the most common, although others occur; *angiomata* involving the renal pelvis or the pyramids are infrequent, but should not be forgotten as possible causes of hematuria. *Sarcomata* of the kidney are not



Section through bladder wall. Tissue hardened in corrosive sublimate, infiltrated with paraffin, stained with hematoxylin and eosin. Section prepared by Prof. H. F. Harris. Drawing made by Miss E. G. Harding. (⅔ in. obj.: 1 in. eye-piece.)

A.—Vascular margin of ulcer showing distended blood vessels. E.—Same.

B.C.D. Tubercles showing beginning breaking down with overlying sloughs.

F.—Submucosa showing intense round-cell infiltration and thickening. The cellular infiltration is most abundant.

G.—Section of the muscular wall. Attention is called to the rather abundant infiltration of round cells.

H.—Serous and subserous layer, which to the left of "I" has been largely denuded. (NOTE.—This denudation probably occurred during removal of the specimen.)

L.K.J.—Intensely engorged blood vessels of the subserous tissues, with extensive rhexis.

large, with atrophy of the renal tissue, due to pressure and the retained material in the pelvis. The condition is not produced by sudden occlusion of the ureter, but is dependent, in most cases, upon gradual narrowing or interrupted obstruction of the ureter, such as may arise from kinking, as in the floating and movable kidneys, or pressure on the ureter by tumors, or obstruction by a calculus, or, as stated on a previous page, chronic ureteritis with contraction may so narrow the lumen of the ureter as to induce retention above the point of obstruction. It will be observed that the causes just given act by slowly

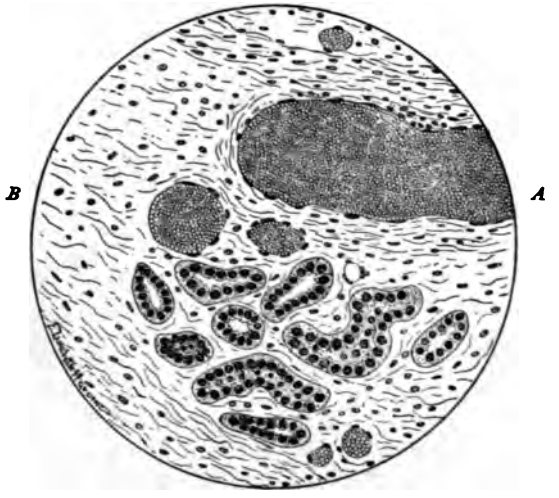


FIG. 293.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. (Tissue from near the pelvis of the kidney shown in Fig. 291.)

A. Distended blood-vessel. *B*. Connective tissue similar to that shown at *C* in figure 295. In many areas this connective-tissue matrix is made up of multipolar or branching cells, such as occur in myxomatous structures. Below the blood-vessels are shown transverse and oblique sections of tubules that resemble, to a certain extent, sweat-glands. (⅙-inch objective, 1-inch ocular.)

inducing an obstruction that fails to permit the escape of secretion as rapidly as formed.

Hydatid cysts of the kidney are rare.

A comparatively infrequent but extremely interesting renal lesion is the so-called **cystic disease of the kidney.** As a rule, but one kidney is involved, except in bilateral congenital cystic disease, when both organs are implicated; such a condition may be sufficiently marked at birth to interfere with delivery. Commonly, the cyst formation begins in the cortical portion of the organ, and, when the subject has survived to

uncommon; they are most frequent in children and young adults. Sarcoma of the kidney may be congenital, and at birth may have attained a size sufficient to impede labor. Although cancers and sarcomata occur as secondary growths in the kidney, they are infrequent.

Cysts of the Kidney.—*Retention cyst* of the tubule, as seen in contracted kidney, has been described. In the cortex they are usually small, although they may be as large as the end of one's

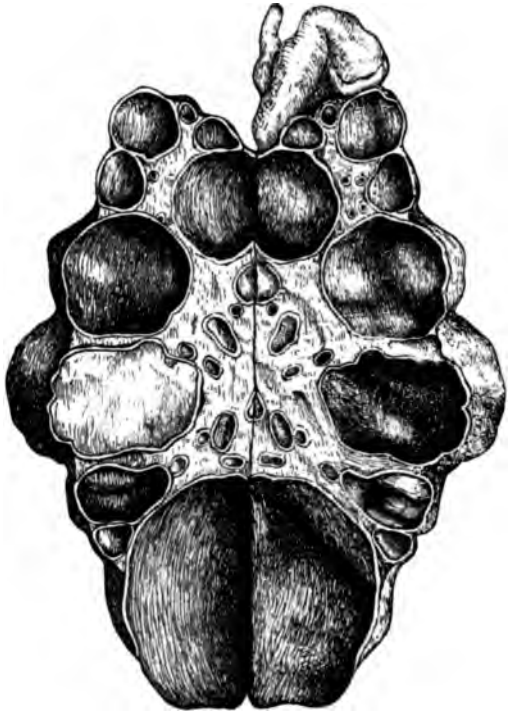


FIG. 292.—KIDNEY, CONGENITAL CYSTIC DISEASE; LAID OPEN. (Same case as Fig. 291.)

thumb, rarely larger; they are usually multiple, occasionally solitary, and are due to the occlusion of the tubule and its dilatation above.

Gradually developing occlusion of the ureter gives rise to **hydronephrosis**, a cyst-like distention of the pelvis of the kidney—a true retention cyst. If the contents of the cyst be pus, the condition is known as **pyonephrosis.** Organs showing either of these conditions vary much in size; they are usually

large, with atrophy of the renal tissue, due to pressure and the retained material in the pelvis. The condition is not produced by sudden occlusion of the ureter, but is dependent, in most cases, upon gradual narrowing or interrupted obstruction of the ureter, such as may arise from kinking, as in the floating and movable kidneys, or pressure on the ureter by tumors, or obstruction by a calculus, or, as stated on a previous page, chronic ureteritis with contraction may so narrow the lumen of the ureter as to induce retention above the point of obstruction. It will be observed that the causes just given act by slowly

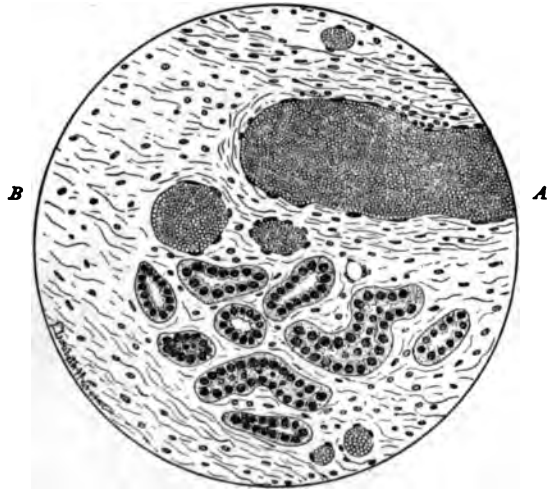


FIG. 293.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. (Tissue from near the pelvis of the kidney shown in Fig. 291.)

A. Distended blood-vessel. *B*. Connective tissue similar to that shown at *C* in figure 295. In many areas this connective-tissue matrix is made up of multipolar or branching cells, such as occur in myxomatous structures. Below the blood-vessels are shown transverse and oblique sections of tubules that resemble, to a certain extent, sweat-glands. (⅛-inch objective, 1-inch ocular.)

inducing an obstruction that fails to permit the escape of secretion as rapidly as formed.

Hydatid cysts of the kidney are rare.

A comparatively infrequent but extremely interesting renal lesion is the so-called **cystic disease of the kidney.** As a rule, but one kidney is involved, except in bilateral congenital cystic disease, when both organs are implicated; such a condition may be sufficiently marked at birth to interfere with delivery. Commonly, the cyst formation begins in the cortical portion of the organ, and, when the subject has survived to

adult life, the cysts may be restricted to that structure. The cystic kidney is large, made up of numerous cysts, and very often shows no recognizable renal tissue; the fluid within the cyst is usually clear, slightly if at all albuminous, and the urinary constituents present are no more abundant than in cysts of other organs. Cholesterin is commonly present, and the cyst may contain a trace of blood pigment, and not infrequently detritus resulting from degenerative and necrotic processes in the epithelium of the cyst-wall. Sometimes the connective-tissue wall of the cyst is not covered by a recognizable epithelial lining. In other instances there is a varying amount of epithelium, which may be granular and necrotic; and in still other specimens low or

FIG. 294.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY.
Section of cyst showing columnar cell-lining and contained detritus; the latter, from a study of other sections, seems to be the fragmented cytoplasm of degenerated epithelial cells cast off from the cyst-wall. The section is from the kidney shown in figure 291. (⅙-inch objective, 1-inch ocular.)

tall columnar epithelial cells form the inner layer of the cyst-wall. A study of these cysts in various stages of evolution would lead to the belief that primarily they all possessed an epithelial lining. The matrix between the cysts may be fibrous or myxomatous, and is not infrequently extremely vascular. The organs may be of normal size or very much enlarged, and they are frequently movable and at times misplaced. The author has in his collection a cystic kidney considerably larger than a fetal head. The organ was removed postmortem from a physician, and during his long and active professional career it had given rise to but slight inconvenience.

Our knowledge of the etiology of these congenital cysts is by no means satisfactory. Virchow believed that they were due to a dilatation of the uriniferous tubules resulting from a possible prenatal inflammatory condition. Goodheart suggested that they were examples of renal adenoma, and in this view was supported by the observations of Bateman. As a result of a careful histo-

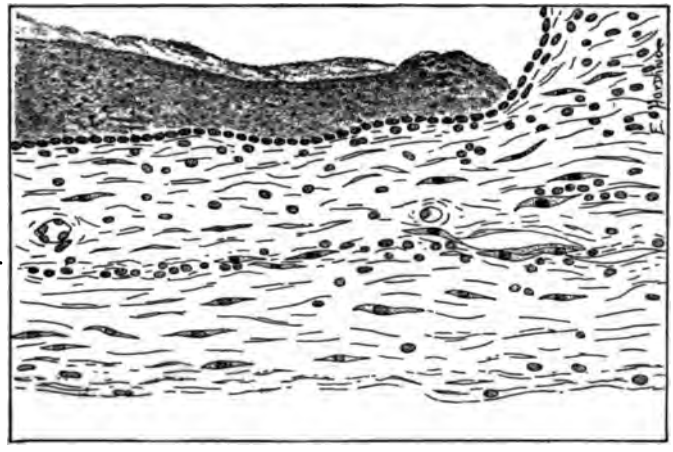


FIG. 295.—CONGENITAL CYSTIC DISEASE OF THE KIDNEY. PART OF WALL OF A LARGER CYST.

Section of the kidney shown in figure 291. *A*. Granular detritus composed of hyaline material and acidophilic granules. *B*. Flattened epithelium. (Compare with columnar cell-lining of smaller cyst, Fig. 294.) *C*. Connective tissue between cysts. (⅛-inch objective, 1-inch ocular.)

logic and embryologic study, Shattock came to the conclusion that the condition depended upon the maldevelopment of the mesonephron, or Wolffian body, fused with the metanephros, and that the cysts resulted from evolutionary changes in the included mesonephron. At the present time the bias of opinion seems to be toward Shattock's view.

CHAPTER X.

ALIMENTARY CANAL.

The **alimentary canal** consists essentially of a tube extending from the lips to the anus, with dilatation at various points for the temporary lodgment of food during the processes of digestion. In the different parts of the canal are glands, the secretion of which promote digestion. The largest of these glands are anatomically distinct from the alimentary canal, but physiologically they are as much a part of the canal as the glands in the mucosa; thus, the essential and important secretions of the mouth are supplied by the salivary glands, all of which lie without the mucosa of the oral cavity; the secretion of the stomach is supplied from glands in its own mucosa; the intestinal mucosa supplies a certain amount of secretion, but the preponderance of secretion utilized in intestinal digestion comes from the pancreas and liver. As each special area in the alimentary canal is dealing with a material the chemistry of which differs from the material in other parts, and as there are important modifications in the anatomy of each region, the diseases of the various areas will also differ.

For convenience in study the alimentary canal is divided into the mouth (including the pharynx), esophagus, stomach, small intestine, and large intestine.

THE MOUTH.

The mucous membrane of the mouth consists of a thick layer of stratified epithelium resting upon a loose and elastic basement membrane, under which is a most abundant submucosa, containing a large quantity of loose connective tissue; this is necessary in order to enable the mucous membrane to adapt itself to the sudden changes in volume that the mouth is constantly undergoing.

Malformations of the Mouth.—The mouth is developed from the branchial arches, failure in the union of which results in the formation of clefts. When the failure of union is restricted entirely to the upper lip and invades the soft parts only, the condition is termed **harelip.** The fissure in the lip is usually directly

below the nasal orifice, and in about ninety per cent. of the cases is restricted to one side. When both sides are involved, the condition is called *double harelip*. As development of the alveolar process and palate is intimately connected with the union of the soft parts forming the upper lip, it is not infrequent, when defects occur in the latter, for them to extend backward and to involve the osseous structure that forms the roof of the mouth. Such a condition is called **cleft palate.** The fissure may be limited to a small niche between the incisors and canine teeth, or it may extend entirely through the hard palate, converting the nasal and oral spaces into one cavity ; occasionally, the failure of union extends still further—a cleft palate becomes **cleft face.** A median fissure situated in the lower lip, and comparable in a certain way to harelip, is occasionally observed, although statements to the contrary are often made.

More or less faulty development of the arch forming the inferior maxilla may result in a cleft at the chin or in entire absence of the bone—a condition known as **agnathia.** This malformation is likely to be associated with cyclopia. Closure of the fissure that enters into the formation of the mouth, when more marked than usual, gives rise to **microstoma.** Failure to close to the usual degree leads to the formation of an unusually large mouth, called **macrostoma.** Arrests in development may give rise to fistulas, through which the mouth or pharynx may communicate with the external surface by some abnormal route. Occasionally, passages which were originally complete fistulas close at one or both ends, thereby giving rise to incomplete fistulas or to closed cavities in which cystic dilatation may occur.

Tongue-tie (*ankyloglossia*) consists in a shortened condition of the frenum of the tongue.

Inflammation of the mouth is known as **stomatitis,** and may be catarrhal, pseudomembranous, gangrenous, hemorrhagic, or suppurative. (For morbid anatomy, morbid histology, etc., see Inflammations of Mucous Membranes, p. 536.)

Follicular stomatitis is an inflammatory process in which the follicles or mucous glands are the seat of the most active inflammation, with the development of vesicles, and with closure, and finally distention, of the ducts, which may terminate in coagulation necrosis of the upper layer, giving rise to small ulcers.

Ulcerative stomatitis, also known as *putrid sore mouth*, occurs in weak, debilitated children, and occasionally in adults ; improper feeding and failure to keep the mouth clean may cause it ; chronic poisoning, such as lead, mercury, or phosphorus, may induce this condition. It occasionally shows a disposition to be

contagious, and this suggests the possibility of its being due to a specific germ, which, however, has not been demonstrated, although successful inoculation on the healthy gum has been practised.

It usually begins as an ulcerative process involving the gum, and is therefore sometimes termed *phagedenic gingivitis.* It spreads superficially along the gum, and gives rise to loosening of the teeth, which may drop out. The ulcers rarely involve the mucosa of the tongue and cheek; the base of the ulcer contains a grayish-white slough; the accompanying catarrhal inflammation, with decomposition of the inflammatory products and necrotic tissue, gives rise to an exceedingly disagreeable, sickening stench, which has given the disease the name of **putrid** or **fetid stomatitis.**

Foot-and-mouth disease is evidently the result of infection, although its exact character has not as yet been determined. The disease is most frequent in ruminants, particularly cows, but abundant evidence has been accumulated to establish the fact that it is communicable to man. The disease is characterized by the occurrence of vesicles on the buccal mucosa, and, although less commonly, on the entire oral mucosa. The inflammation begins by evident hyperemia, with considerable thickening of the corium; vesicles form in the Malpighian layer, eventually forcing off the overlying corneum, which ruptures and exfoliates, giving rise to an ulcer. These ulcers may become confluent and attain the size of one or two centimeters. Many of them consist of simple erosions or of exfoliations secondary to eruption of the vesicle, therefore not meriting the term ulcer. During the progress of the affection in the mouth there is usually more or less fever, and in the lower animals a similar eruption appears in the feet.

Parasitic or **mycotic stomatitis,** or *thrush,* is an infection occurring most frequently in nursing children, and is due to the thrush fungus. (See p. 165.) This fungus does not seem to attack the normal mucous membrane, but becomes engrafted upon a mucosa the surface of which is eroded or irritated by improper feeding or other causes; the disease is occasionally seen in adults after or during acute febrile processes or chronic diseases. The parasite pullulates in the interstices of the epithelium and forms a membrane, usually superficial, but which may extend to the basement membrane, and, by mixed infection, may lead to ulceration. The membranous spots vary in size; at first the diameter rarely exceeds four or five millimeters. The erosion is usually white or creamy white, not easily detached,

and, on microscopic examination, contains, in addition to the specific fungus, many extraneous organisms. The disease usually begins on the tongue, but may arise primarily on, or spread to, the cheek, and thence to the tonsils, palate, pharynx, and esophagus; it differs from the preceding forms of stomatitis in the presence of the germ and in the fact that it is usually associated with marked dryness of the mouth, in contradistinction to the ptyalism that usually accompanies other forms.

Aphthous stomatitis is a disease of childhood, of infancy, and is occasionally observed in adults. The clinical history, the distribution, and, to a certain extent, the lesions indicate a possibly infectious cause. On the mucous membrane small papules appear; these are sometimes converted into vesicles, and later undergo a superficial necrosis, giving rise to what is sometimes incorrectly termed an ulcer. True ulceration—that is, involvement of the connective tissue—is rare. The white, yellowish-white, or grayish erosions may present slightly elevated edges, which may be hyperemic. There is usually more or less infiltration of the adjacent connective tissue, which does not, however, undergo necrosis except in very rare instances. The erosions are located on the inner surface of the lip, although any part of the mouth may be involved.

Gangrenous stomatitis (also known as *cancrum oris* and *noma*) usually begins as a gangrenous process attacking the gums or cheeks, attended by sloughing in the structures involved. The soft parts and bones may become gangrenous and slough, so much so that a greater part of the face may be destroyed by the phagedenic process. The disease usually follows some of the acute infectious processes in children; Osler states that fifty per cent. of the cases follow measles. Girls suffer more frequently than boys. The disease is most frequent between the second and the fifth years; the cases the author has seen have been in older children—from seven to nine years old. The disease usually terminates fatally by septicemic processes. The constancy of the lesion, as well as its characteristics, indicate that the disease is probably mycotic. Lingard has described a thread-like bacillus found in these cases, but not yet fully demonstrated to be the cause. That lowered resistance to infection is an important predisposing factor is shown by the occurrence of noma as a terminal event in tuberculosis during adult life, as observed twice by the author, and in locomotor ataxia.* (See also p. 255.)

* Ness, "Edinburgh Med. Jour.," June, 1899.

Glossitis, or inflammation of the tongue, may be but a manifestation of stomatitis or may be restricted entirely to the tongue. The inflammations involving the surface of the tongue are usually of the catarrhal type. The thickness of the epithelial layers of the mucous membrane, with the irregularity of the papillæ, give rise to a tendency to accumulation of cells that elsewhere

FIG. 296.—LOSS OF TISSUE DUE TO NOMA. (Dr. Moore's case of recovery and subsequent operation reported in the "Intercolonial Medical Journal," of Australasia, vol. III, No. 10.)

The destruction of the soft parts and the necrotic mass of bone with an effort at marginal healing are well shown. Cicatrization is giving rise to ectropion. (Patient aged seven years; the process followed typhoid fever.)

would readily desquamate. The inflammation may be *acute* or *chronic, diffuse* or *circumscribed.* The last is usually dependent upon an irritant that directly affects the area involved, such as the sharp edge of a tooth, an ill-fitting dental plate, the pressure of a pipe-stem, or the injury resulting from long-continued flow

of hot smoke against some part of the tongue. Sometimes the local inflammatory condition gives rise to considerable thickening of the mucosa, the thickened mucosa becoming white or bluish-white in color; the condition is commonly restricted to a small area, to which is applied the term "smoker's patch," or **leukoplakia.**

Inflammation of the tongue sometimes begins in the connective tissue, or that structure may be involved secondarily to superficial inflammation; the condition has received the name **interstitial glossitis.** The process may be chronic and associated with the production of an excess of connective tissue, or it may be an acute suppurative lesion, which in turn is sometimes diffuse, or occasionally accurately circumscribed, giving rise to what is called **lingual abscess.**

Diphtheria usually manifests itself in the pharynx. The inflammations resulting from infection by the bacillus of diphtheria may be catarrhal, pseudomembranous, or gangrenous; in rare cases all three forms must be present in the pharynx, tonsils, or palate. The process may extend upward into the nasal cavities, forward into the mouth, downward into the larynx, or, in rare cases, into the esophagus. (See pp. 541 and 545.)

Catarrhal, pseudomembranous, gangrenous, or *suppurative* processes may arise in the tonsils, palate, or pharynx, as the result of infection by streptococci. From streptococcus, staphylococcus, or other pyogenic infection of the mucosa, submucosa, and cellular tissues there arises a wide-spread cellulitis of the adjacent structures; when this extends into the neck or involves the floor of the mouth, or both, it is known as *Ludwig's angina.* Suppuration around the pharynx, when diffuse, is spoken of as *phlegmon of the pharynx,* or, when circumscribed upon the posterior wall of the pharynx, it is known as *retropharyngeal abscess.*

Tonsillitis.—In the tonsils inflammations are likely to be follicular, associated with occlusion of the ducts, and the accumulation of inflammatory products within the follicles, which eventually break down; catarrhal processes of the surrounding mucosa accompany the follicular lesions. Chronic inflammation of the tonsils is also recognized, and is associated with the overgrowth of both the lymphoid elements and the stroma; new gland structure may be produced.

Of the *chronic infections* that may attack the mouth and pharynx, syphilis, tuberculosis, leprosy, glanders, actinomycosis, and rhinoscleroma occur. (For pathology of these see part II, p. 363.)

Tumors of the Mouth and Pharynx.—An interesting abnormality is sometimes seen at the base of the tongue at a point corresponding to the opening of the thyroglossal duct. This consists in a tumor-like formation composed of more or less normal thyroid tissue. Its unusual position is dependent upon the fact that during fetal life the duct of the gland opened at this point, and ectopic portions of the gland tissue undergoing hypertrophy later in life give rise to distinct tumors of the adult epithelial type. *Papillomata* occur on the tongue and cheek, rarely in the posterior part of the mouth or in the pharynx; *adenomata* occur in the tonsil, and occasionally in the pharyngeal wall. Of the embryonic epithelial tumors the *squamous epithelioma* is the most common; its usual seat is upon the tongue or lips, more commonly the latter; squamous epithelioma of the lip is, of all forms of cancer, the most frequent. Of the adult connective-tissue tumors, *lipomata*, *fibromata*, *myomata*, *chondromata*, *hemangiomata*, and *lymphangiomata* occur. The last of these occur as *macrocheilia*, or lymph lip, and *macroglossia*, or lymph tongue; these conditions are sometimes spoken of as *lymphangiectases*, or dilatations of the lymphatics, in the tongue and lip respectively. Of the *sarcomata*, or embryonic connective-tissue tumors, but few occur in the mouth; myeloid sarcoma of the lower jaw is the most common form.

An **epulis** is a tumor situated on, or springing from, the gum. It may, therefore, be a papilloma, carcinoma, fibroma, sarcoma, or other tumor in that situation. Reference has already been made to pharyngeal and postnasal adenoids. (See p. 555.) A neoplasm of vast surgical and clinical importance is the retropharyngeal sarcoma—a tumor springing from the submucosa or osseous structures of the pharyngeal vault. It apparently reaches a high degree of malignancy, and its peculiar location renders its removal difficult. Endotheliomata of the pharynx and tonsil are infrequent.

SALIVARY GLANDS.

Parotitis, or **mumps**, is an infectious inflammation occurring in the parotid gland. It is, no doubt, due to some form of infection, although exactly what the infectious agent is has not been demonstrated. A chronic infection may occur in any of the salivary glands. The parotid seems more or less susceptible to septic influences, and is not infrequently inflamed during septic diseases, and occasionally in ordinary febrile processes; the condition is referred to as *parotid bubo*.

A similar suppurative condition is sometimes observed in the

sublingual and submaxillary glands. In the last two organs the suppurative process may be secondary to infections of the surrounding tissues. (See Ludwig's Angina.) So far as known, the suppurative interstitial inflammations are the only examples of pure interstitial disease in its acute form affecting these organs.

Chronic Interstitial Parotitis (*Parotid Sclerosis, Fibroid Parotid, Indurative Parotitis, etc.*).—A study of salivary secretion made by Dickinson, who frequently catheterized the duct and showed that often the salivary output was materially below the normal, and the histologic studies made by Harris, who

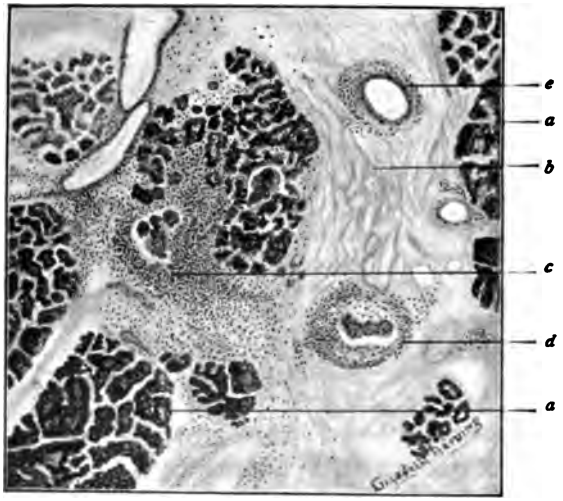


FIG. 297.—SECTION FROM RIGHT PAROTID.* (Carbol-toluidin-blue and eosin. Bausch and Lomb, ⅔-inch Oc. B.)

a, a. Normal lobules. *b.* Thickened trabeculæ. *c.* Cellular infiltration into a lobule. *d.* A duct the wall of which is thickened and infiltrated with cells, and the lumen decreased in size. *e.* An artery with cellular infiltration into its walls.

demonstrated the chronic fibroid changes in the salivary glands, all point to the fact that, like the pancreas, liver, and kidney, these organs are liable to chronic interstitial overgrowth comparable to that seen in the other organs just mentioned. (See Figs. 297 and 298.)

Hypersecretion, sialorrhea, or **ptyalism** is occasionally noticed in inflammations of the mouth as a result of chronic

* Case reported by H. F. Harris, M.D., in the "Boston Medical and Surgical Journal," May 18, 1899.

poisoning by mercury, phosphorus, or copper, and as a physiologic result of the administrations of jaborandi and certain iodin compounds; it is also present in hydrophobia and in other diseases, both acute and chronic, primarily or secondarily involving the nervous system: *e. g.*, hysteria, trifacial neuritis, optic neuritis (?), and sometimes late in tabes. The reverse of the preceding—dry mouth, aptyalism, *xerostoma*—has been observed; the exact cause, however, is not known; it is said to be a symptom of diabetes.

Salivary calculi occasionally form in the salivary ducts, and may, by inducing inflammation and suppuration, perforate the

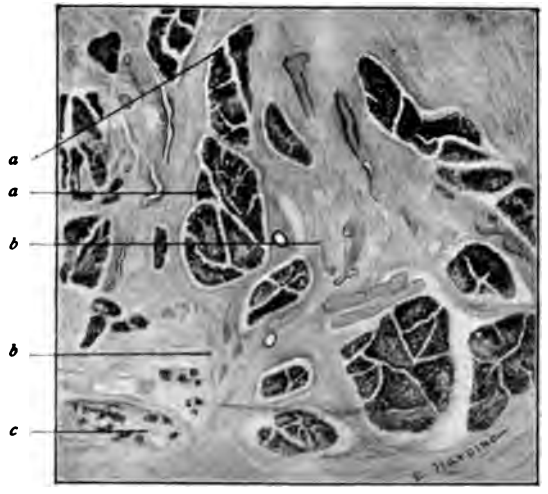


FIG. 298.—SECTION OF THE LEFT PAROTID UNDER A VERY LOW POWER.* (Carbol-toluidin-blue and eosin.)

a, *a*. Normal lobules. *b*, *b*. Greatly thickened trabeculæ. *c*. Lobule almost entirely changed to fibrous tissue. The process is more recent in figure 297.

cheek and form a new tract, which is, of course, a fistula. These calculi are usually composed of the carbonate and phosphate of lime, and are rarely large or very firm.

Obstruction to the duct of a salivary gland gives rise to a retention cyst known as a **ranula**; these are usually named after the gland involved, as *ranula submaxillaris*, *ranula retromaxillaris*, and *ranula sublingualis*. The classic ranula, so long con-

* Case reported by H. F. Harris, M.D., in the "Boston Medical and Surgical Journal," May 18, 1899.

sidered a cyst of the duct of Wharton, is now believed to be a mucous cyst in the Blandin-Nuhn gland.

Tumors of the salivary glands are not common. Of the adult epithelial type, *adenomata* occasionally occur; they are, however, exceedingly rare. Of the embryonic epithelial tissue tumors or cancers, *epitheliomata* are the most frequent, and these, histologically, are usually of the tubular variety, although squamous epithelioma has been observed. *Encephaloid* and *scirrhus* are rare. Of the adult connective-tissue tumors, *chondromata*, *fibromata*, and *myomata* occasionally occur; perhaps the most frequent tumor of the salivary glands is the fibro-adenoma of the parotid. It is not, however, a common growth. Other connective-tissue neoplasms have been observed. The embryonic connective-tissue tumors, *sarcomata*, are at times observed.

ESOPHAGUS.

Normal Structure.—From the pharynx to the anus the essential structure of the musculomembranous tube—the alimentary canal—is that of a mucous membrane resting upon a muscular wall composed of two or more layers of unstriped muscle-fiber. The variations at different points usually consist in different glandular and epithelial layers, but the esophagus differs in its muscular layer from the remainder of the tube, in that the upper part possesses little or no unstriated muscle, while the muscle present in the lower end is, like that in the remainder of the alimentary canal, composed exclusively of unstriped fibers. The epithelium of the esophagus is stratified throughout.

Malformations.—Very rarely, the organ may be absent. Occasionally, from faulty union of clefts, there may be *fistulas*. *Atresia* may result from failure of the two segments of the tube to coalesce. Under such circumstances the lower segment may communicate with the trachea. On the other hand, after complete coalescence obliteration is possible. *Diverticula* or, the reverse, *stenoses* are occasionally found.

Anemia of the esophagus is usually a part of general anemia. **Hyperemia** occurs in the initial stage, and accompanies inflammation of the organ. **Congestion** is marked in the venous distention of chronic heart disease and pulmonary obstruction, such as emphysema and fibroid pneumonia. A condition closely allied to congestion is **varicosity of the esophageal veins.** This is usually dependent upon venous obstruction in the liver, as observed, for example, in cirrhosis. Anastomosis between the lower esophageal veins and the veins of the stomach affords

egress for the blood, which would otherwise be forced to pass through the contracting liver. Rupture of the dilated veins in the esophagus may give rise to fatal hemorrhage.

Inflammations.—*Esophagitis* usually results from injury. The catarrhal form may arise by extension from the continuous mucosa above. Pseudomembranous and gangrenous inflammations are extremely rare. The thick epithelial layers render the infections less frequent than one might expect. *Thrush* of the esophagus has been observed, and is usually secondary to a similar process in the mouth. *Peri-esophageal suppuration* occurs as the result of injury, diseases of adjacent structures, and pyemia. *Syphilis* is the most frequent chronic infection, and usually manifests itself as a gummatous or fibroid change, leading to stricture. Tuberculosis may affect the esophagus as a primary infection or it may extend to the tube from adjacent structures, as the vertebræ behind or the lymphatic glands in front. In other cases tuberculosis is clearly a secondary infection of a syphilitic or cancerous mass in the esophagus that has exposed the connective tissue and favored implantation of the tubercle bacillus. Actinomycosis of the esophagus has been observed. Tuberculosis, actinomycosis, and particularly syphilis, may cause esophageal stricture.

Catarrhal, *hemorrhagic*, and *gangrenous* processes follow the application of corrosive substances, such as strong acids, alkalies, and cauterants, mercury, salts of copper, etc.; scalds and burns induce similar changes. The severity of the process varies, and depends upon the agent used, the concentration, the length of time it acts, and the age of the patient. The young, tender mucous surfaces are specially prone to suffer. Ulceration may follow, should the patient survive, and contraction of the healed ulcers may cause stenosis.

Acquired stenosis of the esophagus occurs in two forms:

1. **Esophagismus** (*spasmodic*, *hysteric*, or *inorganic stricture*) arises as (*a*) a manifestation of hysteria, or as (*b*) a reflex phenomenon due to excessive irritability. A tender point in the esophagus—a minute abrasion or an ulcer—is so sensitive that as soon as touched by a bolus of food, or by an instrument used for exploration, spasm ensues, and only relaxes after considerable force is continuously applied for some time.

2. **Organic stricture of the esophagus** is a narrowing of the tube, independent of muscular contraction, and due to disease. The narrowing may be a single annular band or the stricture may be several inches in length. There are two places in the esophagus where stricture is most frequent: the upper area of

election is just behind the cricoid cartilage ; the lower, opposite the bifurcation of the trachea.

The *causes* may be cicatrization following injury, as that of burns, scalds, or escharotics ; contraction and occlusion incident to the growth of cancer ; or syphilis.

There is a form of esophageal stenosis, called *simple stricture of the esophagus*, that does not seem to be properly grouped with either of the foregoing. There is much doubt as to its origin, although it has been suggested that it is a developmental defect. It is a diaphragm-like narrowing, composed of an annular fold of the mucous membrane, and usually situated near the stomach ; it may be caused by cicatrization of a peptic ulcer, although it is usually held that cicatricial tissue is absent. (See Peptic Ulcer of the Stomach, p. 652.)

Stricture of the esophagus gives rise to **esophageal obstruction**, for which there are many other causes : *e.g.*, foreign bodies lodged or wedged in some part of the tube ; polypoid tumors of the esophagus (rare) ; pressure on the esophagus from tumors of surrounding structures, as mediastinal sarcoma, aneurysm of aorta, swollen lymph-glands, tuberculosis, or other disease, of the vertebræ. Pressure obstruction may occur at any point ; the points of stricture obstruction have been indicated.

Acquired dilatation of the esophagus is always secondary to some other process. It has been known to follow spasmodic stricture. Organic stricture, or any form of obstruction, is likely to lead to dilatation above the point of narrowing. The sac may be fusiform, globular, or, in rare cases, may extend in one direction, forming a diverticulum. A form of dilatation occurring without obstruction, and supposed to be due to atony of the pharyngeal muscles, has been described ; the esophagus in such cases is fusiform, and the point of obstruction is located at or near the cardiac orifice of the stomach. Diverticula, or localized saccular dilatations, occur as the result of lesions in the submucosa, softening that structure and the muscular wall ; the mucosa is then, by internal pressure, forced through the point of softening. Such diverticula occur in the lower part of the pharynx, and are spoken of as **pharyngoceles.** Small, funnel-like diverticula are occasionally noticed in the lower part of the esophagus, near the bifurcation of the trachea, and on the anterior surface. These are due to traction by adherent cicatrices.

Perforation of the esophageal wall may occur, from within outward, in ulcerative processes, as in cancer and in ulceration following injury and lodged foreign bodies. Extensive laceration, with infection of the esophagus by a bougie, is not so rare

as it should be. Perforation from without may result from wounds ; peri-esophageal suppurative processes ; and pressure, as from tumors, aneurysm, goiter, etc.

Tumors of the Esophagus.—Adult epithelium : *Papilloma* occurs, but *adenoma* is very rare. Embryonic epithelium : *Carcinoma* is the usual tumor of the esophagus. The form most frequent is the *squamous epithelioma*, although all varieties of cancer may involve the esophagus.

All forms of connective-tissue neoplasms are rare, although of the adult type *fibromata*, *myxomata*, *lipomata*, and *myomata* occur. *Sarcoma* as a primary growth is rare ; but few cases have been reported. When sarcoma reaches the esophagus, it is usually by extension from contiguous tissues.

STOMACH.

Normal Structure.—(1) External or serous coat. (2) Middle or muscular coat, made up of three layers of unstriped muscle-fiber : the outer layer is directed longitudinally ; the inner is arranged obliquely, while the circular fibers are between the oblique and longitudinal layers. The circular fibers are most abundant near the pylorus. (3) *The mucosa :* the muscular and serous layers are elastic, while the mucosa is less so, as a result of which it lies in folds and elevations when the organ is empty. The submucosa is abundant and loosely woven. The epithelium of the stomach is cylindric, but as it enters the ducts of the glands it becomes shorter and eventually cuboid. The glands are of two kinds—one predominating at the cardiac end, in structure both simple and branched, and containing columnar, cuboid, ovoid, and central cells ; the other glands, predominating at the pylorus, are also simple and branched, but differ from the preceding in that the neck or duct is longer and that the ovoid or parietal cells are absent.

During life the mucosa is pink, occasionally red, but postmortem it assumes a much darker hue ; this is most marked in the dependent portion, and may be mistaken for evidence of disease or injury. Immediately after death, gastric digestion continuing, more or less destruction of the wall of the stomach may result. The mucosa, which has undergone partial or complete digestion, is converted into a soft, pultaceous, transparent, or blackish pulp. The process is most marked in the dependent portion, and may extend through the gastric wall and involve the adjacent structures, even perforating the diaphragm.

Malposition and Malformation of the Stomach.—In the *situs inversus* and in fissural malformations of the abdominal wall or diaphragm the stomach may be transposed, or, in the latter instance, may be forced through the fissure and become more or less extra-abdominal. At birth the stomach may be lower in the abdominal cavity than is normal. Sometimes the displacement is of the stomach as a whole, and is, therefore, comparable to the acquired gastroptosis described later. In other cases the dislocation is of the pyloric end only, giving rise to the so-called *vertical stomach*. *Stenosis of the pylorus*, or even complete *atresia*, may occur. *Sacs*, *abnormal septa*, and *circular constrictions* have been found.

Aside from the foregoing congenital malpositions, certain *acquired displacements* of the organ are not infrequently met with. Enlarged or dilated stomachs are particularly prone to a downward displacement. Tight lacing and spinal curvature are said to favor the occurrence of prolapse of the normal stomach. Mr. Treves takes the view that such malposition is not of necessity associated with any disease of the viscus. The descent of the stomach as a whole, from any of the causes just mentioned, is called **gastroptosis** or *descensus ventriculi*.

Megastria and **megalogastria** are names applied to unusually capacious stomachs showing no abnormality with a possible exception of their enormous size.

Hyperemia of the stomach is a physiologic process during digestion, and also occurs during the initial stage of acute inflammations. The intense distention of the blood-vessels of the stomach and other abdominal viscera during the chill stage of the malaria paroxysm has been variously placed, some regarding it as a visceral hyperemia, and others believing that the increased amount of blood depends upon the venous accumulation. It is not improbable that both factors are operative.

Congestion of the stomach is often marked in cardiac and pulmonary diseases associated with venous stasis, and as a result of cirrhosis of the liver; congestion may precede, accompany, or follow gastroptosis. An intense congestion has been mistaken for the lesions of a destructive or escharotic poison.

Hemorrhage from the Stomach, or Hematemesis.—*Causes.*—Vomiting of blood may be the result of congestion, whether due to portal obstruction, as in cirrhosis of the liver, or to cardiac disease. In the intense hyperemia of acute inflammations and the vascular distention of severe chills, as in malaria, hematemesis is occasionally seen. Sudden changes in blood pressure are presumed to account for the hemorrhage into the

stomach, as a result of hanging, strangulation, epileptic seizures, and allied conditions; it may be that retching or ineffectual efforts at vomiting are truly the cause. Trauma, cancer, ulcer, poisons, and severe retching, as in the vomiting which accompanies poisoning, may induce hemorrhage. It may be vicarious. Constitutional diseases and specific infections, such as smallpox, yellow fever, purpura, and profound anemia, may be complicated by hematemesis. Aneurysm of the aorta may rupture into the stomach. Blood may be vomited that originally came from some other structure, as the blood swallowed during operations on the mouth; also in hemoptysis, epistaxis, and esophageal hemorrhage; in nursing infants the blood may have been sucked from the mother's breast. Aneurysm, varicosity, and possibly other disease of the gastric vessels occasionally act as causes. Rarely, no cause can be demonstrated.

Morbid Anatomy.—The blood is usually clotted, has not the red, frothy appearance of the blood of hemoptysis, is acid in reaction, and may show partial digestion—that is, be black, greenish, or "coffee ground." Postmortem, many of the lesions may be evident,—as cancer,—but often a most careful search for minute ulcers, small ruptured aneurysms, or varicose veins will yield no satisfactory explanation of the hemorrhage. There may be no blood in the stomach, but tarry material may be present in the intestine.

Gastritis (*inflammation of the stomach*) may be catarrhal, either acute or chronic, pseudomembranous, hemorrhagic, or gangrenous. Suppurative processes in the gastric wall—phlegmonous gastritis—are rare, and occur as submucous abscesses or as a diffuse interstitial suppuration, in pyemia and allied conditions.

In addition to the inflammations that apparently begin in or are restricted to the mucosa, there occurs a chronic indurative process located in the muscular and serous coats, and giving rise to most marked thickening of the gastric wall. It has been held that it is due to an extension of inflammation from the mucosa; in some cases, however, the overlying mucous membrane has not appeared to be the site of an associated inflammation, and, hence, the progressive thickening and fibrosis of the wall have been held to be due to an *interstitial gastritis*, and have received the names gastric sclerosis or cirrhosis and fibroid induration of the gastric wall.

Tuberculosis and **syphilis** occur, but are very rare. (For pathology of inflammations of the mucosa see p. 536.)

Mycoses of the stomach occur as (1) infections of the contents by nonpathogenic bacteria, such as the sarcinæ and yeasts,

and as (2) infections of the wall (*mural implantation*), such as thrush, diphtheria, anthrax, and tuberculosis.

Neuroses of the stomach include those manifestations not associated with any demonstrable organic or structural lesion: certain forms of gastralgia, hysteric manifestations, rumination or merycism, etc.

Gastric dilatation, or **gastrectasis,** or *dilatation of the stomach*, occurs in two forms: (1) *Acute*, due to gorging or overdistending the stomach, and (2) *chronic* dilatation. The latter results from (*a*) obstruction at the pylorus, (*b*) atrophy, relaxation, or atony of the muscular wall. In the first group the stomach wall may be thickened as the result of the resistance that must be overcome in order to expel the gastric contents—a compensatory hypertrophy of the muscular coat. In the second group the wall is thin and the mucosa usually atrophied; the cause is here to be found in repeated overfeedings, catarrhal conditions, or general wasting diseases.

Pyloric obstruction may result from healing of ulcers and contraction, from fibroid thickening, from cancerous processes involving the pylorus, rarely from adenoid deposits, from pressure from without,—*e. g.*, cicatricial bands, tumors, as cancer of the pancreas,—and from floating kidney. Gastroptosis may lead to traction on the pylorus, and induce mechanical stenosis. Obstruction may be congenital, or, rarely, foreign bodies may induce it.

Peptic ulceration, perforating gastric ulcer, *simple ulcer of the stomach*, or *round ulcer*, is here described, although an identical process occurs in the duodenum and a closely allied condition in the esophagus.

Causes.—It is not probable that the ulceration is dependent upon any single cause, but rather upon a combination of conditions. The fact that the ulcer develops only in areas to which the gastric juice may have access would indicate that its action is of importance. It is usually held that the ulceration is brought about by some necrosis or by some condition tending to necrosis, and that the actual destruction of tissue is favored by the digestive action of the gastric secretion. Embolism or thrombosis; inflammations of the mucosa, more particularly the hemorrhagic and gangrenous inflammations; injury (?); congestion, such as accompanies cirrhosis of the liver and chronic heart disease, may cause ulcer of the stomach. Predisposing to ulceration are profound anemia, any systemic condition that greatly lowers the body nutrition, and hyperacidity of the gastric secretion. Burns and scalds of the skin have been assumed to

be both predisposing and exciting factors in the production of duodenal ulcer. (See p. 143.) The ulcer is more frequent in females than in males, and is rare, although not unknown, during infancy and childhood. Cade * reported the presence of a gastric ulcer in an infant two months old.

Morbid Anatomy.—Commonly the ulcer is solitary, but as many as thirty-four have been reported as being present at one time; the ulcers are frequently of different ages, a fact that has led to the recognition of two forms—*acute* and *chronic*. In the stomach peptic ulcers are usually near the pylorus, on the posterior wall, close to the lesser curvature. They vary much in size, and are usually funnel-shaped, although they may have deeply undermined edges. They not uncommonly implicate large vessels, and violent hemorrhage may, therefore, accompany them. The edges are usually smooth and regular, but may be terraced, thickened, or indurated, and, rarely, serpentine; induration is marked in the more chronic ulcers. The floor of the ulcer may be smooth, it may present the normal structure of the exposed tissue, muscle, or peritoneum, or evidences of attempted healing may be shown in poorly developed flabby granulations; it may be formed by a part of an adjoining organ, the gastric wall having entirely disappeared; by such attachment perforation into the intestine or colon may occur, or, rarely, communication with the surface or the thoracic cavity may take place. Perforation into the peritoneum is not uncommon (3.2 per cent. of the cases). Should healing occur, a puckered cicatrix results; and if near the pylorus, stenosis may ensue.

Tumors of the Stomach.—Adult epithelium: *Papilloma* and *adenoma* occur, but are rare. The malignant adenoma of the German writers is truly a form of carcinoma. Embryonic epithelial neoplasms or cancers of the stomach are the most frequent tumors. They are most frequent near the pylorus, but there is no part of the stomach exempt. In rare cases they are secondary. The majority of the growths are *cylindric-cell epitheliomata;* next in frequency are *scirrhus*, *encephaloid*, and *colloid*, in the order given. Metastasis occurs in nearly all cases. The adult connective-tissue tumors are infrequent: *fibromata*, *myomata*, and *lipomata* have been observed. Embryonic connective-tissue tumors (*sarcomata*) are rare.

* "Rev. Mens. des Malad. de l'Enfance," Feb., 1898.

INTESTINE.

Normal Structure.—The intestine is lined throughout by a single layer of cylindric cells; the submucosa is abundant and richly vascular. Situated in the mucous membrane of the small intestine are small, isolated areas of lymphadenoid tissue, constituting what are known as solitary glands; when these are agminated, the resulting masses are known as Peyer's patches. For increasing the absorbing surface of the mucous membrane it is thrown into villi and folds; these also increase its liability to injury and disease.

Malformation and Malpositions.—These may be congenital or acquired. Of the congenital, narrowing, or **stenosis**, and imperforate areas, or **atresias**, occur; the latter are most commonly situated near the anus. The canal may be abnormally long or the reverse. Occasionally, a diverticulum situated about one meter above the ileocecal valve is found; this is known as *Meckel's diverticulum*, and is due to the faulty closure of the omphalomesenteric duct; this may remain as a blind pouch or may open externally at the umbilicus. In fissural deformities of the abdominal wall the intestine may be extruded, causing a form of prolapse or hernia. Of the acquired deformities and displacement strictures due to disease, twisting of the bowel, knotting of the bowel, and hernia occur.

Hernia.—The terms hernia and rupture are applied to conditions in which a viscus or part of a viscus protrudes from the cavity in which it is normally contained. As commonly used, the term hernia means a protrusion of the intestine or the omentum through or into some part of the abdominal wall. A hernia is composed of a sac, the contents of the sac, and its covering. Usually, the *sac* is made up of the peritoneum, which is forced before the misplaced viscus. As a rule, at some point in its course the sac is narrowed; the area of narrowing is usually a constriction situated in the abdominal wall, and is called the *neck of the sac*, the *body* being that portion external to the constriction. The *covering of the sac* depends upon the location, and usually consists of the skin and the various underlying fasciæ. The sac usually contains intestine (*enterocele*), or omentum (*epiplocele*), or intestine and omentum (*entero-epiplocele*). Occasionally, a hernia may contain the bladder, stomach, large or small intestine or parts of both, appendix, ovary, etc.

Causes.—Of the many causes alleged to be operative in the production of hernia congenital weakness or defects in the abdominal wall are most important. Such defects are most com-

mon in the inguinal, femoral, and umbilical regions. An unusually long mesentery, as in enteroptosis, coloptosis, or gastroptosis,—splanchnoptosis,—predisposes to hernia. Weakening of the abdominal wall as a result of cicatrices, overdistention, muscular atrophy, etc., favors the occurrence of hernia. Muscular exertion that increases the intra-abdominal tension is usually termed an exciting cause; such effort is typified in straining at stool, lifting heavy burdens, etc.

Hernias are said to be *reducible* and *irreducible*, depending upon the possibility of returning the displaced viscus to the abdominal cavity. Reducible hernias may become *incarcerated* as a result of accumulation of feces in the intestine with or without the presence of gas. Incarceration is, however, more frequent in irreducible hernia. As a result of overdistention or contraction of the ring or neck of the hernia, inflammation, or other causes, arrest of the circulation may occur, giving rise to what is called *strangulated hernia.* A division of hernias into *internal* and *external* is sometimes made. The former include those in which displacement of the viscus is not recognizable externally: for example, diaphragmatic and retro-abdominal hernia. External hernias, as the name indicates, are those in which there is recognizable an external tumor. The division is arbitrary, as many of the so-called external hernias may not be sufficiently marked as to be recognized except by operation or postmortem. With regard to the site, hernias are said to be inguinal, femoral, umbilical, ventral, lumbar, obturator, sciatic, perineal, pudendal, and diaphragmatic.

Obstruction of the bowel may result from the contraction of any inflammatory exudate that encompasses the organ. Malignant disease—most commonly scirrhus, although other forms of cancer, and even sarcoma—may cause obstruction. The intestine may be obstructed by foreign bodies, such as coins, and by gall-stones. Adhesions between coils of the intestine, between the ovary or Fallopian tube and some other organ or the abdominal wall, the attachment of the free end of a Meckel's diverticulum, and the attachment of the appendix to some other organ may give rise to loops or openings through which a coil of the intestine may prolapse, and later become incarcerated or strangulated, exactly as in hernia. Obstruction may also arise from malformations and malpositions, twisting of the bowel (volvulus), tumors of neighboring organs pressing on the bowel, accumulations of fecal matter, and **intussusception.** In the latter condition a portion of the intestine is invaginated within a part below. The intussusception is always from above downward; as

to site, it is most common at the ileocecal valve (*ileocolic*), but occurs also in the ileum (*ileal*), colon (*colic*), ileum and colon (*ileocecal*), or in the rectum. As soon as intussusception takes place, interference with the circulation occurs in that part of the bowel invaginated; this is followed by infection; inflammation ensues, and, in favorable cases of unrelieved intussusception, the invaginated portion sloughs and may be passed with the stools,

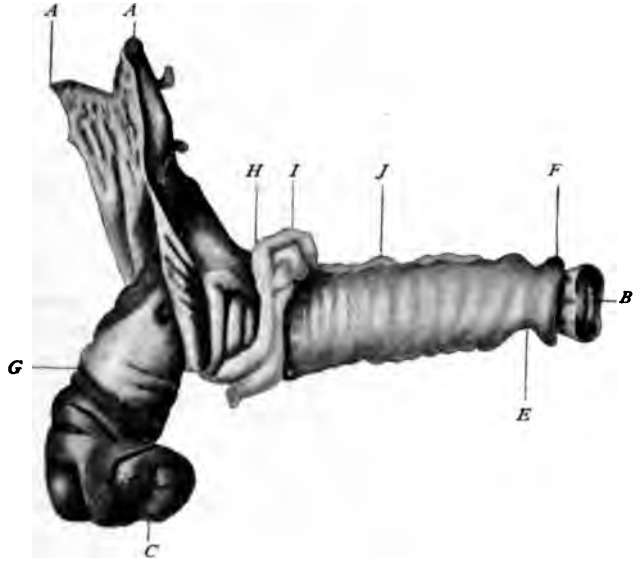


FIG. 299.—INTUSSUSCEPTION AT ILEOCECAL VALVE. (Drawing of specimen from Dr. Graham's case of intussusception; operated on by Dr. Hearn.) (Compare with Fig. 300. The letters have the same significance in both figures.)

A, *A*. Colon. *B*. Point where the ileum enters the intussusception. The leader from the letter *B* points directly within the intestinal lumen. A probe passed in at *B* comes out at *C*; the diagram illustrates the course that it must pursue. *E*. The point of constriction of the ileum. *F*. Point of slight eversion where the serous coat turns to pass within the bowel. *G*. Shows the line of constriction in the ileum caused by the ileocecal valve. The specimen has been pulled through the valve to show this line of constriction and the gangrenous mass of intestine beyond, extending from *G* to *C*. This point of constriction in the diagram is indicated by a slight depression at *G*. *H*, *I*, and *J* show the line of attachment of the mesentery. Between *H* and *I*, and extending slightly beyond the line *I*, is a fold produced by pulling the intestine through the ileocecal valve sufficiently to show the gangrenous process. Scale, one-half the natural size.

and recovery may occur. Repair takes place by an exudate of fibrinous material and the adhesion of the two serous surfaces (see p. 481) at the point where the invagination begins. Should this adhesion be imperfect, perforation of the intestinal wall and infection of the abdominal cavity take place. If the adhesion is perfect, a fibrous cicatrix forms, which, as organization and contraction ensue, may give rise to a stricture.

Intestinal obstruction may be complete or incomplete and may be acute or chronic. In the acute form, and in the chronic, if complete, gangrene of the intestine is likely to follow, favoring the occurrence of perforation and peritonitis.

Dilatation of the bowel may result from anything obstructing the passage and favoring occlusion; atony of the muscle is a cause; chronic constipation also acts as a cause. Gradually developing obstruction or stenosis may give rise to dilatation. The

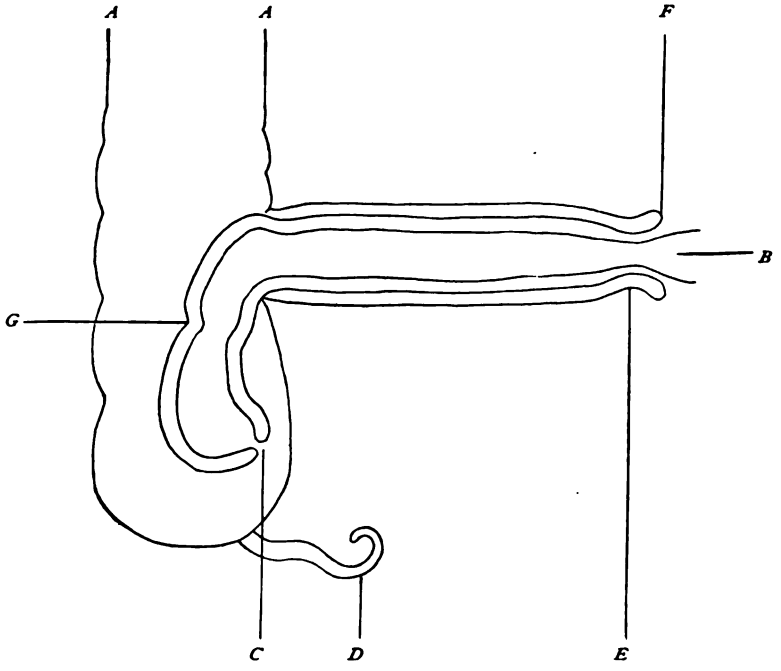


FIG. 300.—INTUSSUSCEPTION DIAGRAM INTENDED TO SHOW THE RELATION OF THE SEVERAL PARTS IN FIGURE 299.

The outlines of the caput coli and of the appendix have been added in order to indicate more clearly the relations. *D*. The appendix. The letters have the same significance as in figure 299.

colon may be extremely capacious, especially in chronic obstruction. If the obstruction is due to atony of the bowel, the dilated intestinal wall is thin; if the cause is gradually developed, as from a slowly contracting stricture or a malignant growth, the wall will probably be thick, as the muscular layer may have hypertrophied in an attempt to overcome the progressively increasing obstruction.

Inflammation of the intestine may be catarrhal, pseudo-membranous, gangrenous, hemorrhagic, suppurative, or chronic infectious. Pathologically, there is little difference between the lesions of various parts of the intestine in any given inflammatory process. The catarrhal inflammations present the same morbid conditions in different parts, but may give rise to peculiar complications owing to anatomic peculiarities: *e. g.*, catarrhal duodenitis may extend to the bile-duct; catarrhal appendicitis may produce obstruction of the appendix where it empties into the colon, by swelling the submucosa at the narrow point of communication between the two viscera. At times the follicles are particularly the seat of the inflammation, and necrotic processes may give rise to follicular ulcers, or the lymphoid elements that make up a Peyer's patch may be particularly involved. Again, the exudate may be very abundant, as is observed in the severe serous diarrheas; occasionally, the reverse may be the case. The inflammations in the various parts of the intestine have received the following names: Duodenum, duodenitis; jejunum, jejunitis; ileum, ileitis; appendix, appendicitis; head of the colon, typhlitis; colon, colitis; rectum, proctitis.

As previously stated, the pathology of these processes does not differ in any essential manner from that observed on other mucous membranes, for description of which see page 536.

Dysentery occurs as a catarrhal, gangrenous, hemorrhagic, or suppurative inflammation of the colon, although the small intestine may be involved in the morbid process. When due to the amœba coli (see p. 195), irregular, indurated ulcers develop in the colon; these may undermine and coalesce in the submucosa; the undermining is less marked, usually absent, in gangrenous or diphtheric dysentery. In chronic dysentery cicatrices form, ulcers redevelop from time to time, and all possible combinations of inflammatory phenomena may occur. In all forms of dysentery septic and pyemic lesions may arise.

Infectious Processes.—**Cholera**, due to the spirillum of Asiatic cholera (see p. 190), is attended by a most violent serous catarrhal inflammation of the mucous surface. In the later stages follicular involvement may be marked, and ulceration may occur.

Typhoid or Enteric Fever.—More or less marked catarrhal inflammation, with a varying serous and desquamative element, accompany the other intestinal lesions. Early in the disease the lymphoid follicles become swollen and prominent, hyperemic, and occupied by proliferated cell elements and mononuclear leukocytes; rarely, the process is sufficiently intense to cause necrosis and ulceration of the solitary follicles. In the agminated follicles

—the patches of Peyer—the hyperemic swelling and the cell proliferation are more marked and the bacillary infiltration is deeper. The patches are elevated, edematous, and surrounded by a slight zone of redness; at first the patch is intensely engorged and deeply colored, but later the tension within the patch rises, less blood enters, circulation is arrested, necrosis occurs, the slough is thrown off, and an ulcer results. The depth of the ulcer is dependent upon the extent of the necrosis; it may involve only a part of the mucosa, but more commonly the entire thickness of

FIG. 301.—SMALL INTESTINE.—TYPHOID ULCER DURING THE EARLY PART OF THIRD WEEK OF THE DISEASE. (Natural size.)

The long axis of the ulcer corresponds to that of the bowel; the base of the ulcer still contains the slough, or necrotic tissue, which is nearly ready to be thrown off; its ragged and fissured surface is well shown.

the mucous membrane is destroyed and the submucosa or muscularis is exposed. The edge of the ulcer is irregular, swollen, and, it may be, undermined. The base of the ulcer, after the slough has completely disappeared, is clean and smooth. If the sloughing process be attended by vascular stasis in the muscularis, the necrosis may extend through the intestinal wall, or perforation may occur after the slough has been thrown off. If a vessel of any size is opened in the process of sloughing, or if a coagulum fails to form in a necrotic vessel, hemorrhage results. With separation of the slough, in favorable

cases, repair begins; embryonic followed by granulation tissue develops, and epithelial reproduction proceeds from the margins toward the center.

The typhoid ulcer is oval in outline, with its long diameter in the axis of the bowel; it rarely involves the entire patch, but may do so; the ulcers are most abundant and most constant near the ileocecal valve, but may develop in any part of the intestine where the lymphoid elements are present. Chronologically, infiltration and cell proliferation terminate in necrosis about the end of the second week or in the beginning of the third week; during the latter the sloughs separate; healing may not be completed until clinical recovery has long been passed.

With infiltration of the Peyer's patch, and the generation of poisons therein, the lymphatics and blood-vessels begin the absorption of toxins, whose influence may be wide-spread; at the

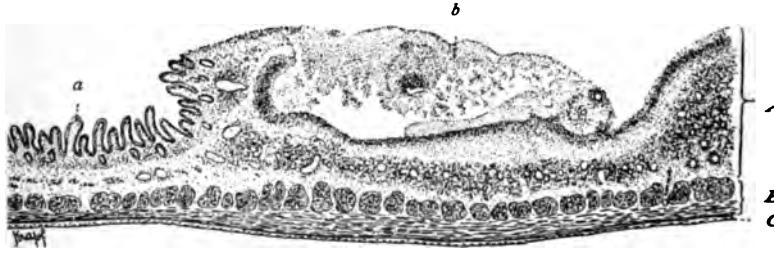


FIG. 302.—SECTION THROUGH A TYPHOID ULCER, END OF SECOND WEEK OF THE DISEASE.—(*Schmaus.*) (Partly diagrammatic.)

A. Mucosa and submucosa, the latter infiltrated with lymphoid cells. *B*. Muscle-coats of intestine. *C*. Serous layer of intestine. *a*. Adjacent nearly normal mucosa. *b*. Separating slough.

same time the bacilli gain access to the viscera, and may be found not only in the patches but in the mesenteric glands, spleen, and liver, and, although rarely, in the blood. The mesenteric glands are infiltrated, and may be necrotic; suppuration due to the pyogenic activity of the bacillus, or to mixed infection by pyogenic cocci, may occur. The adjacent lymphatic glands (retroperitoneal) may be involved.

The spleen is enlarged, soft, and may show infarction, rupture, or gangrene.

The liver shows cloudy swelling, and may contain areas of coagulation necrosis.

The kidneys exhibit a similar change, or may even pass into acute nephritis.

The muscles of the abdomen and the adductors of the thighs

may show hyaline or vitreous degeneration. Rarely, other muscles may be involved. Granular change or cloudy swelling may be present in the cardiac muscle. Inflammatory or even suppurative processes may occur in other organs: *e. g.*, in the parotid glands, in the bones, etc. The cause of these is not always apparent, but they may be due to embolism, or to infec-

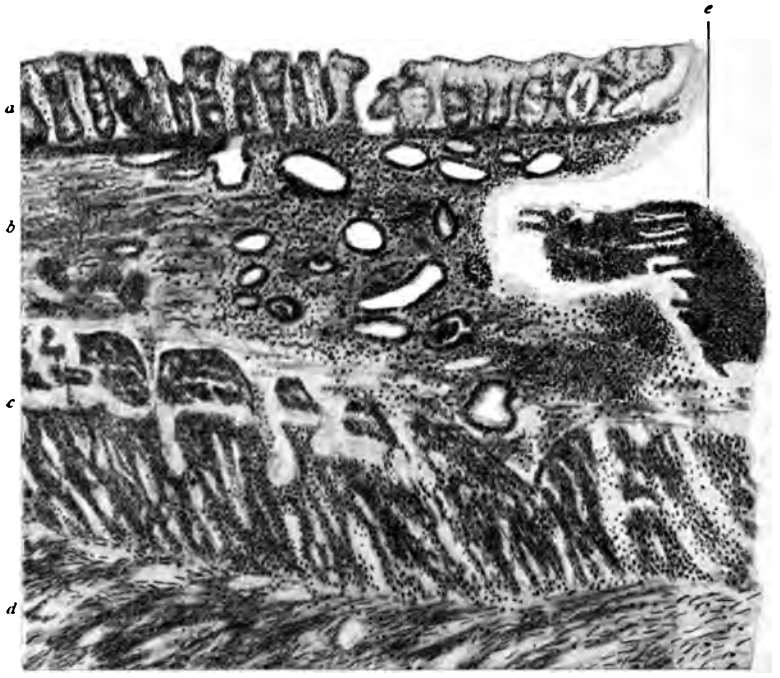


FIG. 303.—SECTION OF THE INTESTINAL WALL AT THE EDGE OF A TYPHOID ULCER, BEGINNING OF THIRD WEEK OF THE DISEASE. (Much higher magnification than Fig. 302.) (¼-inch objective, ½-inch projection ocular.)

Specimen hardened in corrosive sublimate, infiltrated with paraffin, stained in hematoxylin and eosin, and mounted in balsam. *a*. Mucosa, which overhangs the margin of the ulcer. *b*. Submucosa, infiltrated with serum and containing some fibrin. Near the ulcer well-marked and extensive round-cell infiltration is seen. *c*. Transverse muscle-fibers; immediately under the ulcer these will be seen to contain many round cells and show degenerative changes not discernible with this magnification. *d*. Longitudinal muscle-fibers. *e*. Slough of necrotic tissue matted together, and about separated, preliminary to being thrown off.

tion by typhoid bacilli or other bacteria gaining ingress through the open ulcers in the intestine. Infective processes may occur in the portal vein.

Syphilis of the intestine is rare; it usually occurs in the rectum, where a firm fibroid stricture may develop from gummata deposited around the bowel. The stricture develops

slowly, is most common in women, and may or may not be attended by ulceration; most commonly this is absent. (See Stricture of the Larynx due to Healing of a Gumma, p. 559; also Fig. 271, p. 560.) (For description of syphilis of mucosæ see p. 550.)

Tuberculosis of the intestine may occur as a primary or secondary process; it may be miliary without ulceration, or, more commonly, ulcers develop. The tubercles are commonly situated in the adenoid structures; caseation follows; this leads to destruction of the overlying mucosa, and an ulcer results. The ulcer, if of any size, is irregular; its long axis is transverse to that of the bowel; its edges are infiltrated and caseous; and, if examined by transmitted light, tubercles may often be seen in its base. The serous surface is puckered from newly developed fibrous tissue; if the ulcer passes around the bowel, a

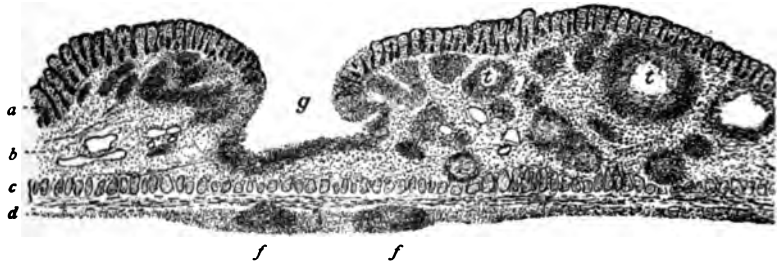


FIG. 304.—TUBERCULAR ULCER.—(*Schmaus.*) × 12 diameters.

a. Mucosa. *b*. Submucosa, in which are numerous tubercles, *t* and *t'*; in the latter, caseation is advanced. *c*. Muscularis. *d*. Serous covering, in which, at *f*, *f*, are two tubercles. *g*. Opening of ulcer into the lumen of the canal.

stricture may be developed; tubercles may be seen in the peritoneal coverings of the intestine; the lymphatic glands are likely to be involved. (For description of tuberculosis of mucous membranes see p. 548; also Fig. 268, p. 549.)

Tubercular abscesses in and around the rectum may give rise to *fistulas*, which may communicate internally with the bowel or externally through the skin or with both the bowel and cutaneous surface.

Leprous nodules and ulcers are occasionally found in the colon, rarely in the small intestine.

Actinomycosis, although infrequent, involves both the large and the small intestines, and an actinomycotic appendicitis has been described.

Tumors of the Intestine.—Of the adult epithelial tumors,

adenomata occur; these may occasionally be pedunculated, although they are commonly sessile; they are usually located in the rectum, and are extremely likely to become cancers. *Papilloma* occurs about the anus, but is rare. Embryonic epithelial tumors are most common in the rectum and colon; they are usually cylindric-cell epitheliomata, although other forms of cancer, including scirrhus, are occasionally found. Squamous epithelioma occurs in the lower part of the rectum near the anus. Of the connective-tissue tumors, *fibromata* and *myomata* are the most frequent, although rare. *Sarcomata* occasionally invade the intestine.

Varicosities of the veins of the rectum, particularly of the hemorrhoidal veins, constitute what are known as *hemorrhoids*.

CHAPTER XI.

LIVER.

Normal Structure and Function.—Essentially, the liver is a mucous membrane in which the connective tissue passing throughout the organ is the basement membrane and the cell elements of the lobules are the epithelium upon which the functional activity of the organ depends. The lobules are formed of hepatic cells arranged in rows radiating from a common center. The blood supply, derived from the portal vein, passes from the periphery of the lobule toward the center; the course taken by the blood from the hepatic artery is of necessity similar, as the blood derived from the two sources finds its exit by the one route—the hepatic vein, which leaves the center of the lobule. The biliary capillaries arise in the lobules, and pass in a direction opposite to that taken by the blood. The lobule is the gland unit and the hepatic cell is the cell unit. The gland differs from all other glands in its blood supply: there is the usual arterial supply, represented in the hepatic artery; to this is added the portal supply—an enormous volume of blood, brought from the digestive canal, laden with the products of food metabolism. The portal vein is distributed to the periphery of the lobule, and the zone immediately adjacent is known as the *portal vein zone*; in the center of the lobule is the hepatic vein, draining the blood from the lobule, and the tissue immediately surrounding this is known as the *hepatic vein zone*; between the two areas just indicated lies a zone called the intermediate or *hepatic artery zone*. Histologically and physiologically, these zones are not differentiated; but disease processes, as will be seen later, outline them in a more or less well-marked manner.

The lobule is surrounded by connective tissue, which is continuous with that of the median fissure and the capsule, and is known as the capsule of Glisson; in this the portal vein, the hepatic artery, and the bile-ducts ramify, and these carry into the lobule enough of the connective tissue for support. In man the lobule is not sharply differentiated, and a number of lobules appear confluent. By confluence or juxtaposition many lobules form a lobe, and these lobes constitute the organ. The portal

vein, representing the collected blood from the alimentary canal and spleen, is of itself a circulation, in the sense that there is a capillary system at either end. It differs from the other blood systems, pulmonary and systemic, in that, between the two capillary areas—the one in the intestine, stomach, etc., and the other in the liver—there is no propelling body, and the blood must flow, in this subsidiary circulation, by reason of the cardiac force distributed to the capillary system in which the portal vein finds its origin. Pathologically, this is of the greatest importance, for when the general circulation is feeble, whenever there is a tendency to stagnation, to venous stasis, how unfortunately situated is the portal system to escape the inevitable result! When the blood leaves the surface, as in the chill of malaria, and there is a tendency to distention of the veins, those of the portal circulation are most prone to suffer. So it is that obstructive diseases of the lung or heart, which impede the onward flow and favor stasis in the veins, evince their most marked phenomena in the hepatic and digestive structures.

Physiologists have agreed that the liver performs the following functions:

1. *Hematolytic* or *hemolytic:* Disorganization of blood elements is necessary to the production of bile coloring-matter, and it is generally believed that this hemolysis is, at least partly, carried on in the liver, or begun in some other organ, as the spleen, and completed in the hepatic tissues.

2. *Secretory:* Bile is not only eliminated by the liver, but is manufactured by the hepatic cells.

3. *Urea production:* The liver is believed to be influential in the production of urea.

4. *Glycogenic:* Glycogen is manufactured in the liver.

5. *Antitoxic:* The interception of poisons.

The latter has been demonstrated of strychnin, in which a dose by the stomach or injected into the hepatic blood supply may be much larger and less injurious than similar doses given by the systemic circulation. Toxicologists also recognize the filtering influence of the liver, in that poisons may be recognized in that organ when not discoverable elsewhere.

Malformation and Deformity of the Liver.—Malformation of the liver at birth is not common. Rarely, the liver may be absent. Increase or diminution in the number of the lobes is occasionally observed; the gall-bladder may be absent, partly developed, or ductless, the duct having been occluded after the formation of the diverticulum, from which the bladder is later developed; with absence of the gall-bladder there may be some dilatation of the

hepatic duct. Acquired deformities, not due to disease, are usually the result of pressure: *e. g.*, by light lacing, the wearing of tight belts, pressure from tumors in adjacent structures, etc.

Malpositions of the liver are rarely congenital; the organ may be transposed, as in the *situs inversus;* laxness of the ligaments may give rise to what is known as the *hepar mobile*, or *floating liver;* occasionally, a liver is found that is so attached by its ligaments as to permit rotation on its transverse axis, at times presenting its edge forward and again its broadest aspect, thus, by altering the area of dullness, misleading the clinician; in the same way a liver may be so suspended as to always present its broad surface, and thereby appear large, or by always presenting its edge it may appear small. *Acquired malposition* may result from pressure from above, as in pleuritic effusion of that side; it may follow the waist deformity produced by lacing; or be caused by marked spinal curvature. Displacement upward resulting from the contraction of a fibroid or cirrhotic right lung, or increased intra-abdominal pressure, or any other cause acting in a similar manner, is not, of necessity, a cause of disturbance of other digestive organs.

Hyperemia of the liver is physiologic during digestion, and is by some believed to be constant in diabetes.

Congestion of the liver results from any condition that retards the venous circulation and slows the blood in the inferior vena cava; the most frequent causes of this condition are valvular heart disease, especially mitral disease, and pulmonary obstruction, as in emphysema, chronic bronchitis, etc. The retarded circulation backs into the thin-walled hepatic veins, which, being most distensible within the lobule, gradually dilate, and by pressure lead to atrophy of the adjacent liver-cells; the zone around the hepatic vein is first affected, and, histologically, may be made up entirely of dilated branches of the hepatic vein, with complete destruction of those hepatic cells lying immediately around the central vein. The retarded circulation favors the infiltration of fat, and the margin of the lobule may contain such an excess of fat that it appears distinctly yellow to the naked eye.

Macroscopically, the organ is much larger than normal, and may attain considerable size; that this is largely a vascular distention is shown by the fact that when the veins pulsate, the liver may also manifest this phenomenon. The organ is red, hence the name **red atrophy**, and, on section, oozes considerable blood; the lobules can usually be made out, and the dark-red center of each lobule, with its lighter periphery, resembles a transverse section of a nutmeg, and hence the name

nutmeg liver. In some cases there may be considerable increase in the connective tissue. While the organ during life may be much larger than normal, when removed and drained of blood it shrinks and presents a wrinkled capsule, and is much lighter than its size would indicate.

Hypertrophy of the liver is infrequent except as a compensatory process. When one lobe or one part of a lobe is destroyed by disease, increase in the amount of the residual hepatic structure is usually observed; thus, in atrophy of one lobe or a part of a lobe as a result of pressure, or in destruction of one lobe by abscess or cyst, if the patient fully recovers, hypertrophy of the remaining liver tissue may occur.

Atrophy of the liver arises from several causes:

1. **Simple atrophy of the liver,** due to starvation or inanition: *e. g.*, in the writer's collection is a liver weighing about 560 gm., taken from a patient who died slowly, from starvation, as the result of cancerous disease of the esophagus. In such cases, associated with general atrophy, the liver may be reduced to one-third of its normal dimensions and weight. The process is probably both simple and numeric, and begins at the periphery, where the evidences are most marked; every part of the organ, however, is implicated.

Morbid Anatomy.—Such a liver possesses a sharp margin, and is darker in color than the normal organ; the relation of lobes, one to another, is normal; after removal from the body and when drained of its blood, the capsule is wrinkled, because the remaining liver-cells no longer fill it; the gall-bladder frequently projects from three to seven centimeters beyond the margin of the liver. The blood supply to the organ is poor in nutrition; the absence of food from the alimentary canal excludes the normal stimulus to secretion, and, as a result of the combined conditions, very little bile is produced.

Morbid Histology.—The diminution in size of the lobules is extremely marked; the liver-cells are small, atrophied, usually stain indifferently, and are frequently pigmented; there seems to be as much fibrous tissue as liver structure, but this is probably due, not to an increase of fibrous elements, but to a diminution in the size and number of the hepatic cells.

2. **Pressure atrophy of the liver** covers a multitude of lesions. Women who lace tightly, by pressing in the margin of the ribs, produce a deep groove or impression in the larger lobe of the liver, and may almost completely divide it; the same result is accomplished in men who wear tight belts, as is so frequently done by a certain class of laborers. The liver is very

susceptible to pressure, and is, therefore, influenced by neoplasms in adjacent organs, and by tumors and accumulations of gall-stones or accumulated secretion or inflammatory matter in the gall-bladder.

Another form of atrophy from pressure is **red atrophy,** which has already been discussed; the pressure is exerted in this form of atrophy by the blood dammed back into the liver lobule, thus compressing the cells and leading to their disappearance. (See Congestion of the Liver, p. 666.)

A certain amount of atrophy accompanies amyloid infiltration, in that the new deposit in the liver interferes to a certain extent with the function of the adjacent cells. Cirrhosis of the liver, by compression of the lobules, also leads to atrophy. Obstructed bile-ducts give rise to pigmentation and atrophy of some of the cells. In all forms of atrophy of the liver more or less pigmentation of the organ is commonly present; besides the pigmentation incident to atrophy, the lesion itself interferes with the production, and may also obstruct the escape, of the bile (*acute yellow atrophy*). (See p. 672, also Jaundice, p. 234.)

Infiltrations to which the liver is liable are: (1) Fatty infiltration, (2) amyloid infiltration, and (3) pigmentary infiltration.

Fatty infiltration of the liver arises as the result of an abundance of fat, sugar, or alcohol supplied to the organ; in all of which cases the liver acts merely as a storehouse for the temporary deposition of the nutrient element not needed by the system at large; a certain amount of fat is normal, and is essential to the elaboration of perfect bile. Those causes just cited represent nothing but an excess of the normal.

Fatty infiltration of the liver is also found in those diseases in which oxidation is in abeyance. As an example of this form, may be mentioned the fatty infiltration found in consumption, cachexia, anemia, and allied conditions. The lesion produced by phosphorus-poisoning is held by some to be a fatty infiltration, and by others a fatty degeneration; it is possibly a combination of the two processes.

Morbid Anatomy.—The liver of fatty infiltration is enormously increased in size, and is usually the largest liver seen in the post-mortem room; it is firm, with its margin rounded, its capsule smooth, pale in color, bloodless, even on section, and when incised with a moist, clean knife, distinctly greases the blade. While the organ may weigh from three to four kilograms, its specific gravity is low, owing to the amount of fat that it contains; the added fat being lighter than water, the organ may have a specific gravity of 1000. The gall-bladder does not ex-

tend to the margin of the organ ; the bile is usually lighter in color than the normal, but clinically there is no evidence, in ordinarily fatty livers, that the bile is deficient in functional activity.

Morbid Histology.—In fatty infiltration in the earlier stages the fat will be found distributed in the periphery of the liver lobule, occupying largely the portal vein zone (Fig. 305) ; in extremely advanced cases the infiltrated area may approach the center of the lobule, but not until the margin is extensively invaded. The fat exists, usually, as a single large globule in the liver-cell, crowding the nucleus to one side (see Fig. 176, p. 227) ; the nucleus is frequently apparently normal in structure and in stain reaction. Liver-cells adjoining those containing large quantities

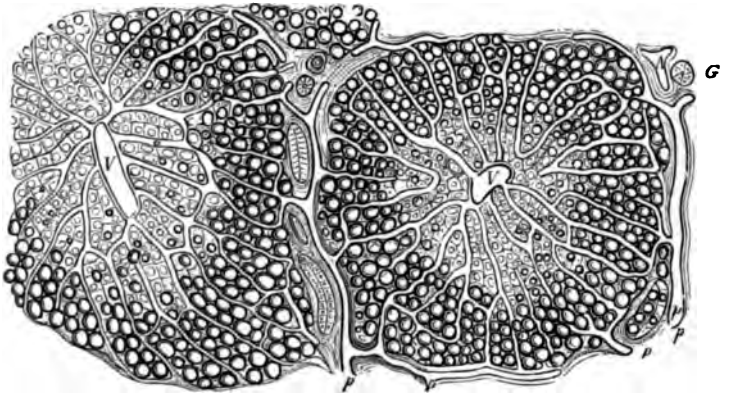


FIG. 305.—FATTY INFILTRATION OF THE LIVER.—(*Rindfleisch.*) (Semidiagrammatic.)
V, V. Hepatic vein, around which are many normal liver-cells. *p, p, p, p, p.* Ramifications of the portal vein that bring the products of digestion directly to the periphery of the liver lobule, into which the fat is infiltrated as large globular collections of oil within the liver-cell. *A.* Hepatic artery. *G.* Bile-duct.

of oil are, as a rule, uninvolved ; granular or cloudy change in the unaffected cells is rarely present, thus differentiating the liver-cell of fatty infiltration from the same structure in fatty degeneration. (See Fatty Infiltration, p. 225.)

Amyloid or albuminoid infiltration consists of an infiltration into the liver of the so-called lardacein. The infiltrated agent is deposited in the intermediate or hepatic artery zone of the liver lobule ; the causes are those of amyloid infiltration in general. (See p. 228.)

Morbid Anatomy.—The organ is very much increased in size, its margin rounded, its capsule smooth and free from thickening ; the tissue is firmer and more elastic than normal, contains little

fat, and is pale and bloodless; the cut surface responds to the chemic and stain reactions commonly given by amyloid material. (See p. 250.)

Properly prepared sections show the lardaceous material more or less irregularly distributed in the intermediate or hepatic artery zone of the liver lobule. The branches of the hepatic artery show the usual lardaceous deposit in their walls.

Pigmentary infiltration of the liver occurs in connection with chronic malaria, and is associated with other lesions that give the organ the name of *malarial liver*. The cause of the process evidently lies in two conditions: (1) The repeated

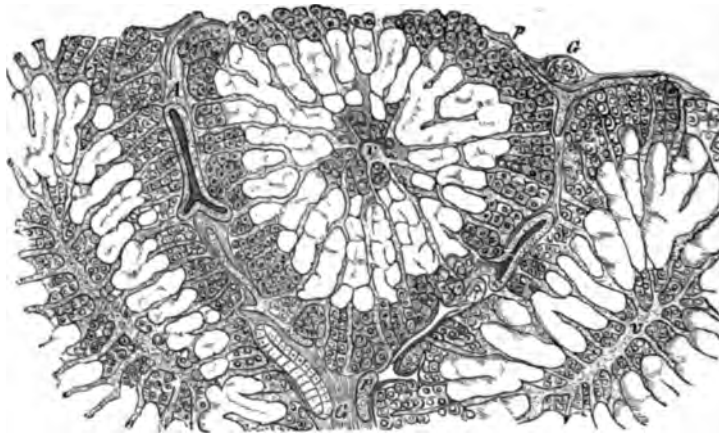


FIG. 306.—LIVER, AMYLOID INFILTRATION.—(*Rindfleisch.*) (Semidiagrammatic.)

A. Branch of hepatic artery with lardaceous walls. *G*, *G*. Bile-ducts. *p*, *p*. Portal veins. *v*, *v*. Hepatic veins. Parts of three lobules are shown. In the center of the lobule, immediately surrounding the vein (hepatic vein zone), and at the periphery of the lobule (portal vein zone) are many, but slightly altered, liver-cells. The intermediate area (hepatic artery zone) is occupied by amyloid material, which has taken no stain and appears as a homogeneous, almost hyaline, body.

engorgement occurring as a result of the malarial paroxysm, the liver being enormously distended with blood at each chill; and (2) the hematolytic changes induced by the malaria parasite liberates the coloring-matter (hemoglobin), which, after important changes, is finally deposited in the hepatic tissues. The pigment circulating in the blood is deposited in the liver tissue and gives rise to the peculiar color by which the organ is readily recognized.

In pigmentary infiltrations of the mucous membranes, such as anthracosis, the pigment may reach the liver and be deposited in the connective tissue that surrounds the portal vessel, giving

rise to a certain amount of pigmentation of the organ. (See Pigmentary Infiltration, p. 231.)

Morbid Anatomy.—During life, when distended by blood, and when the process is not combined with cirrhosis, the organ is larger than normal; postmortem, it is usually smaller, but the rounded margin and wrinkled capsule indicate that the shrinking has been a postmortem process. Usually, the wrinkled surface can be rendered smooth by stretching. The color is a grayish-brown or slate-color, due to the deposited pigment; this grayish-lead color has given the organ the name *slate-colored liver.* The liver is more or less flabby or flaccid, resists incision more than the normal organ, and, on section, oozes considerable blood and pigmented serum; the gall-bladder is small and does not come to the margin of the liver, while the contained bile is likely to be thick and ropy. Under the microscope a blackish pigment is found disseminated throughout the organ, around the lobules, and in the perivascular intralobular structures; this is altered blood coloring-matter (melanin). Associated with the pigment deposit there is likely to be considerable increase in the connective tissue; this may be so great as to constitute an actual cirrhosis; the newly formed connective tissue may be found not only between the lobules, but in the lobules.

The foregoing description applies particularly to the hepatic enlargement of chronic malaria. If death occur early in the infection, pigmentation is, of course, less marked. The malaria parasites may be present in the organ, particularly in the estivo-autumnal fever. Necrotic areas associated with, or independent of, capillary thrombosis are occasionally observed.

The degenerations most frequent in the liver are parenchymatous and fatty.

Parenchymatous degeneration of the liver is found in connection with high temperatures, septic and other infectious processes, and in many intoxications. (See p. 241.) The organ is swollen, is usually pale, and the cut surface is cloudy and opaque, not shining and translucent like the normal; with the granular change in the epithelium of the lobules there is not infrequently more or less necrosis, usually coagulative in character. The bile elaborated by such an organ is deficient, and may be physiologically inert.

Morbid Histology.—The liver-cells are granular (Fig. 182, p. 242) and show the initial changes observed in the beginning fatty degeneration. By some it is believed that the change is one of beginning catarrhal inflammation of the lobule, analogous to that observed on the mucous surfaces in the stage of catarrhal inflam-

mation when desquamation is impending; the belief that the degenerative and necrotic changes constitute a part of an inflammatory process has led to the condition under consideration being called **parenchymatous hepatitis.**

Fatty Degeneration of the Liver (also known as *Acute Yellow Atrophy of the Liver*, *Malignant Jaundice*, and *Icterus Gravis* *).—The cause of this condition is not known, but the feeble tendency to epidemicity, the fact that the etiologic agent attacks individuals in groups,—*e. g.*, many cases occur in a single locality among the pregnant women,—taken with the character of the symptoms and lesions, indicate a possible infectious agent. The disease is most common in women, and usually occurs between the ages of twenty and thirty. As before stated, the changes induced by phosphorus and arsenic are analogous, but not always identical. Some observers are inclined to regard the process as inflammatory; others, as a purely degenerative change depending upon the destruction of hepatic tissue by a poison the exact nature of which is unknown.

Morbid Anatomy.—The organ is much reduced in size and weight, is flabby, and in advanced cases may be folded over upon itself; as a whole, the consistency may be almost that of a bag of fluid—semifluctuating; the capsule is wrinkled. The color is not uniform; on the surface and in section will be observed areas dirty yellow in color, varying in size, and irregular in form; around and between these patches the liver is red, cloudy, and usually firmer. While the organ may resist incision, the semifluid condition of its contents is shown by the fact that large quantities of hepatic tissue may be extruded through a small opening. There may be hemorrhage into the organ, although this is more common in other viscera than in the diseased liver.

Under the microscope the changes to be observed are most marked in the yellowish areas already described. The liver-cells are indistinct in outline and advancedly fatty; all stages of fatty degeneration are recognizable; cloudy and granular cells, and cells containing minute oil globules abound, and occasionally areas occur in which the cells are no longer demonstrable. The fat seen in the liver-cell is both in and around the nucleus (see Fig.

* The terms *icterus gravis* and *malignant jaundice* have been applied to forms of hepatic degeneration associated with, and believed to be secondary to, severe jaundice. They have also been used in the sense indicated here. Of the many synonyms offered for acute yellow atrophy none is fully acceptable. The term *ictère hémorrhagique essentiel*, used by the French, is probably less committal, and therefore more acceptable, than many of the names commonly given.

183, p. 243), and exists as minute drops or oil globules, in contradistinction to the large drops usually present in fatty infiltration. All zones of the liver lobule are invaded in rapid succession, apparently the outer or portal vein zone first. In some cases the connective tissue between the lobules is normal; in others it shows a tendency toward proliferation.

The changes observed in the other organs are hemorrhages, especially from the mucous and cutaneous surfaces; the kidneys are granular, and may be fatty; the spleen is usually enlarged, soft, and congested; and fatty degeneration of the heart may be present.

Coagulation necrosis, as seen in the liver, occurs in typhoid fever, diphtheria, and allied infectious processes; the organ usually shows cloudy swelling; the necrotic areas are minute pin-point spots, whitish or yellowish-white in color, and under the microscope appear as hyaline, degenerated, or dead masses of liver tissue, with fragmentation of the cell nuclei. (See Coagulation Necrosis, p. 250.)

Hepatitis (Inflammation of the Liver).—The difficulty in deciding exactly what constitutes inflammation of this organ, and to what conditions we are justified in applying the term hepatitis, have already been indicated when considering cloudy swelling and acute yellow atrophy of the liver. The admittedly inflammatory processes are (1) the chronic interstitial inflammations that involve the organ, and (2) suppurative conditions. To these possibly might be added (3) the chronic infections to which the organ is liable.

Phlegmonous hepatitis, suppurative hepatitis (*hepatic suppuration*), may be manifested as a more or less diffuse lesion secondary to phlegmonous cholangitis, which will be considered later. (See Biliary Passages, p. 682.) Abscess occurs in the liver as a result of trauma, embolic or pyemic processes, and associated with the presence of amebæ.

1. **Traumatic Abscess.**—When injury has been received over the liver and transmitted to that organ, it is probable that, in the process of repair, opportunities are afforded for the localization of any pyogenic bacteria that may be circulating in the blood, and an abscess is thereby engendered; injury due to bruising, and foreign bodies finding access to the liver—such as pins, needles, fish-bones, etc.—also act as causes by producing infection or by giving rise to an area of reduced resistance favorable for the localization of pyogenic organisms. Cysts of the liver may suppurate after the most trifling injury.

A traumatic abscess is usually solitary, and presents no lesion

distinct from that of abscess elsewhere. It is, of course, associated with bacteria of suppuration. It is probable that the blood present in the liver is richer in bacteria than the blood elsewhere in the body. This is to be attributed to the fact that bacterial ingress would be as likely from the hepatic artery as from the nutrient vessels to other organs, and, aside from this source of infection, the portal circulation offers conditions especially favorable for bacterial ingress. The somewhat sluggish character of the hepatic circulation favors the deposit and colonization of any organisms entering the liver from either source. It may be that in this way the frequency with which trauma engenders hepatic abscess can be explained.

2. **Pyemic abscess** is usually multiple; and when there is a large solitary abscess in pyemia, it is probably due to the coalescence of many small foci. Infected emboli may reach the liver through the hepatic artery or from infected thrombi in the portal vein.

3. **Tropic abscess** is usually solitary (75 per cent. of the cases), although there may be two (10 per cent.) or more (14 per cent.); the lesion is usually situated in the right lobe; the wall has no distinct surrounding membrane: (*a*) The inner layer of the wall consists of necrotic liver tissue; (*b*) an adjoining layer is composed of functionally inactive tissue, in varying stages of necrosis, surrounded by (*c*) a zone of intense hyperemia; unlike the acute and pyemic abscesses, the pus of the amebic abscess may be sterile, and contain the amœba coli (p. 195), to which the abscess is now generally considered to be due. The disease is usually associated with dysentery due to the amebæ, although occasionally the abscess is found without any distinctly antecedent dysenteric attack.

Cirrhosis of the liver is a chronic interstitial inflammation involving the interlobular connective tissue of the organ. (See Productive Inflammation, p. 293.)

1. **Atrophic Cirrhosis** (also known as *Fibroid Liver*, *Granular Liver*, *Gin-drinker's Liver*, *Hobnail Liver*, *Chronic Interstitial Hepatitis*, *and Contracting or Contracted Liver*).

Causes.—Alcohol, syphilis, red atrophy, malaria, chronic infections, scarlet fever, rickets, pigmentary infiltration. Many explanations have been offered for the excessive development of fibrous tissue in and around the lobules in cirrhosis. It has been held to be a reactionary inflammation resulting from an irritant brought to the liver by the portal vein, and this view, in the light of alcoholic cirrhosis, seems not without reason. By some authorities it is maintained that the initial change is degenerative,

the periphery of the lobule being destroyed by some poison, and that the destroyed or injured zone is replaced by embryonic connective tissue, which goes on to complete organization, and later develops contraction. (See Substitutive Fibrosis, p. 293.) Weigert inclines toward the explanation just given.

Morbid Anatomy.—In atrophic cirrhosis of the liver the organ is diminished in size, not infrequently weighing less than one kilogram; the surface is uneven, rough, granular, or hobnailed; the tissue is unusually firm, and offers considerable resistance when incised; on section, it presents a yellow, green, or greenish-yellow color; the gall-bladder is usually slightly diminished in size, and the contained bile is watery and dark, although it may be thick and

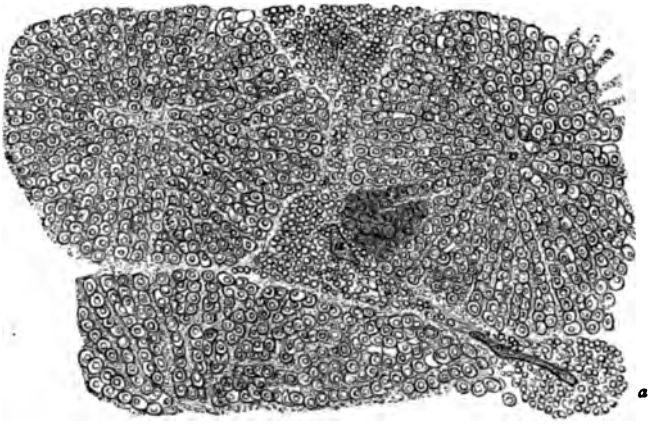


FIG. 307.—BEGINNING CIRRHOSIS OF THE LIVER.—(*Rindfleisch.*) × 300 diameters. *a*, *a*. Interlobular vessels, surrounded by young cell infiltrate. *v*. Hepatic vein.

ropy; the bile is less active than normal, and the atrophy of the gall-bladder would indicate that the quantity is diminished.

Morbid Histology.—There is an enormous increase in the fibrous tissue of the liver, and every lobule, in some areas, may be found surrounded by masses of new connective tissue in various stages of development. Contraction of the newly developed fibrous tissue leads to atrophy of the liver-cells, to diminution in size, and, as the ramifications of the portal vein are embraced in the contracting tissue, there is obstruction to the portal circulation. This obstruction of the portal vein leads to slowing of the circulation in the intestinal and mesenteric branches, to congestion of the intestinal and gastric mucosæ, and to a transudate of serum into the abdominal cavity; so great may be the latter that

the abdominal cavity may contain from two to four gallons of fluid, and repeated tappings may be necessary to remove the serum that results from the venous stasis. (See Causes of Edema, p. 265.) Occasionally, bile-ducts may be obstructed by the contracting tissue, and jaundice may ensue, although this is not a common phenomenon. There is some increase of fat, possibly due to the slowing of the circulation.

In some cases, after long-continued evidence of portal obstruction, as shown by the rapidly developing ascites, the blood may find a short route from the portal vein to some of the systemic

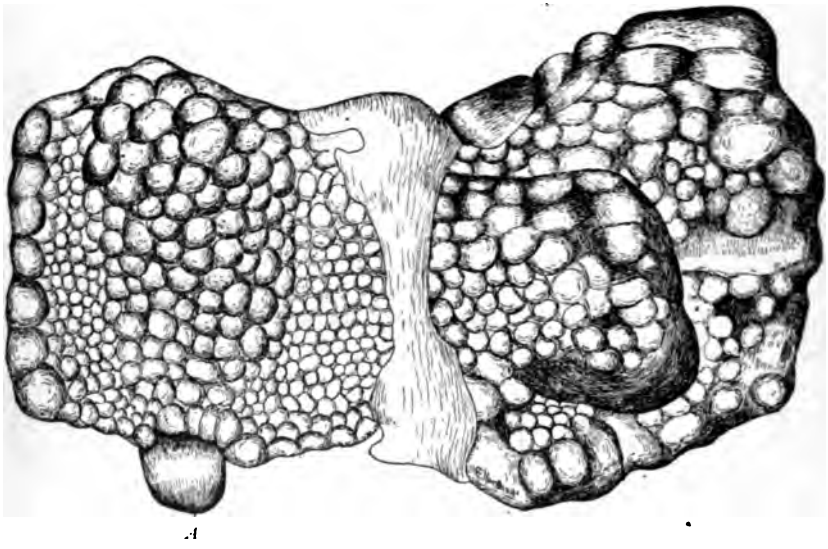


FIG. 308.—SUPERIOR ASPECT OF LIVER, SHOWING UNUSUAL DEGREE OF CIRRHOSIS WITH "HOB-NAILED" SURFACE.

A. Gall-bladder. The patient was a chronic alcoholic and died from gastro-esophageal hemorrhage. (Illustration one-half natural size.)

veins, and thereby avoid passing through the contracting fibrous tissue. This short circuiting, by venous anastomosis, occurs through the very much enlarged (1) gastric and esophageal veins; (2) the veins of the round ligament; (3) the veins in the suspensory ligament; (4) the inferior hemorrhoidal veins; (5) the veins of Retzius; (6) a single vein, or, rarely, more than one vein, just under the capsule, may make a direct traceable connection between the very much enlarged portal vein and the hepatic vein.

2. Fatty Cirrhosis.—In addition to the increase in the connective tissue observed in atrophic cirrhosis, there may be more or less fatty infiltration, giving rise to an organ that but little resembles the preceding.

Morbid Anatomy.—The fatty cirrhotic liver is large and is usually smooth, but may be slightly granular; the surface may be undulating, is distinctly yellow in color, and presents the rounded

FIG. 309.—ATROPHIC CIRRHOSIS OF THE LIVER, ADVANCED.—(*Schmaus.*) × 50 diameters.
a. Liver lobule. *b*, *b*. Newly formed fibrous tissue. *c*. Bile-ducts. *d*, *e*, *f*. Granules or hobnails on the surface of the liver, due to pulling downward of the newly formed connective tissue. If the masses are small, they appear on the surface of the organ as granules; if large, they form hobnails. *g*. Branch of portal vein. *i*. Hepatic vein in center of lobule.

edge, etc., already noted as present in fatty infiltration (see p. 668); on section, however, it is very much firmer, and contains an excess of fibrous tissue as well as of fat; the fibrous tissue is distributed in the same manner as in atrophic cirrhosis and with the same result, except that the extensive infiltration of fat enlarges the organ.

3. **Hypertrophic cirrhosis** is more commonly called *biliary cirrhosis*, and differs from the preceding in that the liver is permanently enlarged and shows no tendency toward contraction; the proliferated connective-tissue cells do not develop into fibrous tissue, but, to a varying extent, retain their embryonic state.

Morbid Anatomy.—The organ is large, much darker than the preceding varieties, and of a greenish-yellow color; the surface is smooth, the margin rounded, the gall-bladder retracted, the tissue firm, and offers marked resistance to incision. The cut surface is usually pigmented and bile-stained, and the newly formed connective tissue is recognizable between the lobules.

There is an abundance of mononuclear cells between the lobules, and even extending into the tissue of the lobule. The bile-ducts appear to be increased in size and number, and the grouped ducts sometimes form adenoma-like aggregations. By reason of the absence of contraction there is little obstruction to the portal circulation, and hence there is no dropsy. The increased interlobular proliferation may obstruct bile-ducts, and commonly gives rise to jaundice.

4. **Glissonian Cirrhosis** (*Hepatic Capsulitis, or Perihepatitis*).—In this form of cirrhosis the liver is diminished in size, the capsule is everywhere greatly thickened, and is firmly fibroid, sometimes almost cartilaginous, in consistency; the thickened capsule can be readily stripped off, leaving almost normal hepatic tissue beneath, although there is some increase in the interstitial connective tissue.

Syphilis of the liver may be a manifestation of congenital infection or may arise during the secondary and tertiary stages of the acquired disease. The lesions resulting from *congenital syphilis* are by no means uniform, nor are they readily divisible into distinct groups. True gummata are infrequent. A more common manifestation is the occurrence of a more or less diffuse fibrosis, associated with the formation of dense fibrous bands (Fig. 311) dividing the organ into irregular abnormal lobes—the *lobulated liver* of congenital syphilis. (See Fig. 310.) With the formation of new fibrous tissue there is not infrequently shown small areas of lymphoid accumulation, which have been designated miliary gummata. In still other cases a diffuse generalized atrophic cirrhosis occurs, resembling that resulting from the continuous use of alcohol. In other cases, sometimes combined with one or more of the foregoing lesions, areas of necrosis in the hepatic tissue can be recognized. It is not impossible that these are manifestations of the destructive influence of the syphilitic poison,

and that by a kind of substitutive fibrosis the necrotic areas become converted into fibrous patches.

In *acquired syphilis* many of the necrotic fibroid changes already mentioned as possible in the congenital type may be found. More or less cirrhosis is not infrequently present, and gummatous masses in various stages of fibroid and hyaline change are occasionally present. The *gummata* seen in the liver vary in

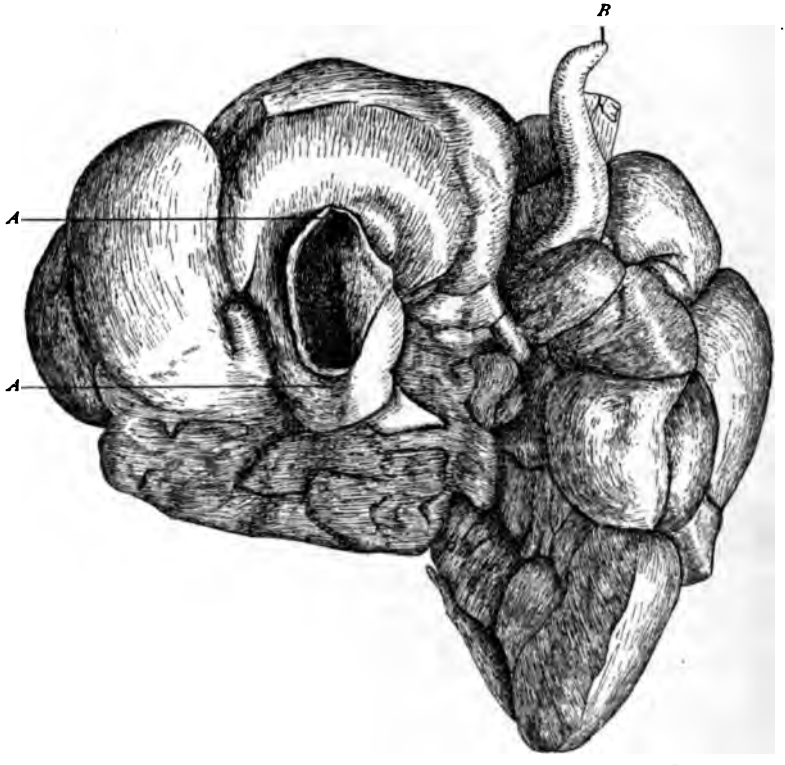


FIG. 310.—UNDER-SURFACE OF LIVER SHOWING RESULTS OF CONGENITAL SYPHILIS. *A, A.* Gall-bladder. *B.* Round ligament. The organ is irregularly fissured in many directions, giving rise to a large number of lobes. The patient from whom this liver was removed died in the second week of typhoid fever; age, seventeen years.

size, and the postmortem appearances are largely dependent upon whether or not treatment has been applied during life; distinct fibrous, depressed, usually stellate cicatrices, showing more or less puckering, and situated immediately under the capsule, are not infrequently the result of the healing of gummata. In other cases the gumma will be found as a soft, hyaline, partly fibroid

or distinctly caseous collection. Gummata may be single or multiple, and evidently of different ages.

Leprosy nodules have been observed in the liver, and present the same characteristics as when seen elsewhere. *Actinomycosis* and *glanders* also occur; they are, however, rare.

Tumors of the Liver.—Adenomata of the liver occasionally occur, and probably arise from the bile-ducts with which they are closely associated. These tumors are commonly cystic; the cyst

FIG. 311.—SYPHILITIC CIRRHOSIS OF THE LIVER.—(*Schmaus.*) × 40 diameters.

a. Liver capsule. *b*, *b*, *b*. Newly formed connective tissue, which is grouped in a band-like area, as at *g*. *c*. Branch of portal vein. *l*, *l*, *l*. Liver lobules. *e*. Deep fissure produced in the liver surface by the traction exerted by the fibrous bundles, *g*.

wall may be papilliferous; occasionally, cystic adenomata are largely composed of dilated bile-ducts. *Coccidial disease* of the liver is constantly associated with the production of such cysts. (See p. 193.) *Cancer* of the liver is usually secondary to similar growths in other abdominal viscera: *e. g.*, stomach, pancreas, intestine, genito-urinary organs. *Primary hepatic cancer* is most commonly a cylindric-cell epithelioma. *Secondary cancer* partakes of the characteristics of the primary growth from which

it disseminated. Of the adult connective-tissue tumors *fibromata*, *angiomata*, and *lymphangiomata* occur; other members of the group are rare. *Sarcomata* occur as primary and secondary growths; the primary growths are exceedingly liable to be pigmented (melanotic).

Cysts of the liver, in addition to those previously mentioned, arise either in the connective-tissue spaces between the lobules or in the lobule or bile-ducts; the so-called *cystoma* of the liver is

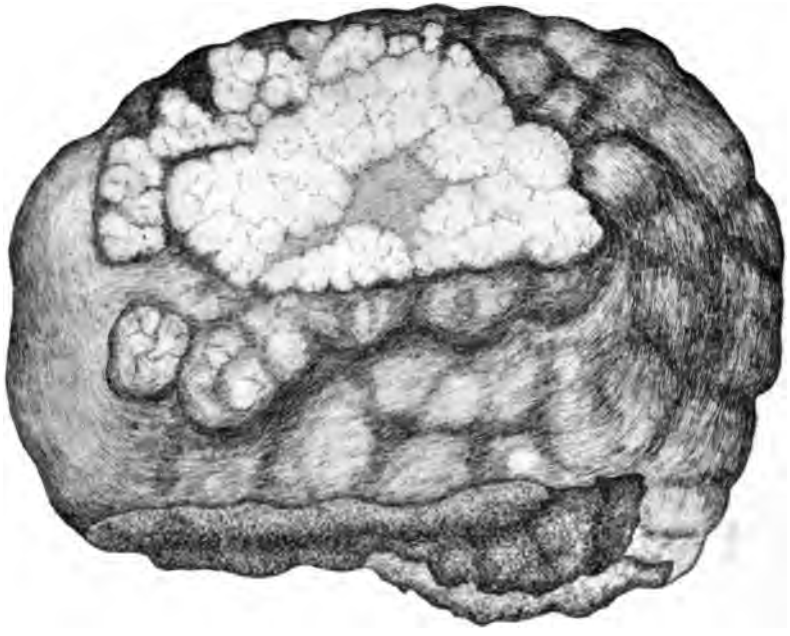


FIG. 312.—PART OF LEFT LOBE OF THE LIVER, SHOWING PRIMARY CYLINDRIC-CELL CARCINOMA.

The slight umbilication of the cancerous nodules is indicated. Figure 202, page 325, is from a section of this tumor. (Removed by Professor Keen from a man fifty years of age.* The illustration is three-fourths natural size. Mass weighed 525 gm. The patient recovered.)

usually a congenital cyst containing colloid or clear fluid surrounded by a wall analogous to a serous membrane. (See p. 360.) *Hydatids* of the liver occur as single or multiple cysts with a structure peculiar to echinococcal disease. (See Parasitic Cysts, p. 362; also forms of cysts produced by the echinococcus,

* For detailed report see "Annals of Surgery," September, 1899.

p. 206.) Occasionally, small cystic dilatations of the bile-ducts result from occlusion of the smaller passages. Rarely, small cysts are found in the liver; they contain a clear fluid, and their walls may be lined by ciliated columnar epithelium.

BILIARY PASSAGES.

Malformations.—Occasionally, the common duct, the duct of the gall-bladder, or the gall-bladder itself may be absent; in certain cases of jaundice in the new-born the ducts are either absent or nonpatulous.

Cholangitis, or inflammation of the biliary ducts, may be a catarrhal process, either *acute* or *chronic*, or it may be *suppurative*, and, in rare instances, *gangrenous*.

The *acute catarrhal inflammations* are commonly secondary to duodenitis, but may also result from the presence of gall-stones or from hydatids, either in the liver or along the course of the biliary passages. Cancer and other tumors obstructing or invading the biliary passages are likely to induce or to be associated with catarrhal inflammation. The changes in the mucosa are those seen in catarrhal inflammations of the mucous membranes. (See p. 536.) In the milder forms of the disease the patients rarely die, and therefore but little knowledge is available as to the changes occurring in the liver. When, however, the condition has persisted for any length of time, the liver is usually enlarged and the connective tissue surrounding the biliary passages shows more or less cellular infiltration. The lobules may contain areas of necrosis.

Chronic catarrhal inflammation of the bile-ducts, also called *chronic catarrhal cholangitis*, arises as a result of the continued action of the causes already given when considering the acute form. The disease usually invades the gall-bladder; it may give rise to obstruction of the cystic duct, and thereby induce considerable dilatation. It is probable that in nearly all forms of cholangitis bacteria may play a certain part. It is, however, in the *phlegmonous cholangitis* that they are most active. The morbid process usually begins as, or is associated with, a catarrhal inflammation, and hence the causes already given for this process are to a certain extent influential. The disease may be secondary to cholelithiasis; it is not infrequently associated with general infections, such as occur in pyemia, pneumonia, typhoid fever, and influenza. The colon bacillus, the typhoid bacillus, and the usual pyogenic organisms are the bacteria most frequently present. As to the course of infection, it is probable that in most

instances the bacteria reach the biliary passages from the intestinal canal by a process of direct invasion. It is not improbable that the infection may occur through bacteria reaching the hepatic tissues by way of the circulation, and, finding in the biliary passages conditions suitable for their growth, lodging and giving rise to inflammation. Phlegmonous cholangitis may arise from, or terminate in, pyemia or septicemia. The suppurative process may be restricted to the gall-bladder (*phlegmonous cholecystitis*), in which condition the wall of the gall-bladder becomes edematous and infiltrated with leukocytes, which may accumulate in the interior in sufficient numbers to justify the conclusion that the contents of the gall-bladder is pus, constituting what is called *empyema of the gall-bladder*. Peritonitis may occur without perforation of the cystic wall, infection having traveled through the lymph-spaces. The gall-bladder is commonly greatly enlarged, and the evidence of the septic character of the inflammation is further indicated by the systemic phenomena attributed to the absorption of toxic bodies from the area of infection. Whether the process began in the gall-bladder or originated in the common duct or its ramifications in the liver can not always be determined. When the biliary system is involved in a diffuse suppurative cholangitis, the liver is usually enlarged, and on section pus may be identified in and around the biliary passages, which not uncommonly show more or less dilatation. If the disease be permitted to progress, or if the patient survive, abscesses, macroscopically recognizable, may be found in the hepatic tissue.

Gall-stones, or **biliary calculi,** occur in the gall-bladder most commonly, occasionally in the common duct, and rarely in the hepatic duct or its branches. Structurally, each stone is composed of a nucleus of bile pigment, inspissated mucus, or bacteria, around which is deposited cholesterin, either in its amorphous or crystalline form. The calculi may be single or multiple, occasionally the gall-bladder containing hundreds of them. They may give rise to obstruction of any of the ducts in which they become lodged, and this may be followed by catarrhal or suppurative inflammation; reaching the bowel, they may lead to obstruction of that viscus. Ulceration, or even perforation, into the abdominal cavity—some hollow viscus: *e. g.*, stomach or colon —and external discharge of the stone occasionally occur.

Tumors of the Biliary Passages.—In the gall-bladder *papillomata* sometimes develop. They are usually of the villous variety, and not infrequently undergo transformation into cancer. Similar tumors terminating in the same manner may occur in the ducts. *Carcinoma* of the gall-bladder and the biliary passages

may be primary or secondary. Primary growths are usually of the *cylindric-cell epithelioma* type, although *scirrhus* and *encephaloid* are occasionally observed. The cancers are frequently associated with cholelithiasis, and it is held that the irritation produced by the gall-stones leads to cancerous development. *Myomata*, *lipomata*, and other adult connective-tissue neoplasms may develop in the wall of the gall-bladder or biliary ducts. *Sarcomata* are rare and are usually secondary. *Retention cysts* involving the gall-bladder or biliary passage usually result from impacted calculi, although similar dilatations may be brought about by gradually developing stenosis, which may be cicatricial in origin or due to the pressure of inflammatory masses, tumors, etc., or to cancer. The recent retention cyst of the gall-bladder or biliary passage is distended with bile. In the course of time, particularly in the gall-bladder, the biliary character of the cyst contents is no longer demonstrable. The material distending the sac is mucous or watery, and the condition is called *dropsy of the gall-bladder*. Purulent accumulation in the gall-bladder constitutes what is called *empyema*. A dilated gall-bladder may contain little or no fluid, being distended in such cases by calculi. Similar distention by calculi in the biliary duct is at times observed.

CHAPTER XII.

PANCREAS.

Normal Structure.—Histologically, this organ is a reproduction of the salivary glands, consisting of acini, with smaller ducts emptying into a larger duct (Wirsung's duct), the latter terminating in the duodenum in common with the hepatic duct.

Malformations and **malpositions** of the organ are infrequent. The tail of the pancreas may be pulled out of position by a misplaced spleen, to which reference has already been made. (See p. 450.) In Glénard's disease (visceroptosis or enteroptosis) there may be a slight downward displacement of the organ, but it is not, however, marked. Tumors and cysts occupying the retroperitoneal tissues may push the pancreas forward. Cancers involving the posterior surface of the head of the organ may render it distinctly palpable.

Hyperemia of the pancreas is normal during digestion and occurs in the initial stage of the acute inflammatory processes that affect the organ.

Congestion of the pancreas may be a part of a general abdominal congestion, and is most marked in the presence of a long-continued obstructive lesion within the heart, or may result from cirrhosis of the liver.

Hemorrhage into the pancreas (*pancreatic apoplexy* or *pancreatic hemorrhage*) is now a recognized morbid process. Little is known of the cause of the condition; it may occur at any age, but is most frequent in middle life and later. It is occasionally associated with evidence of congestion, to which it has been attributed. It is alleged that the continued use of alcohol favors its occurrence. It is probable, however, that the alcohol is only indirectly responsible for the process, causing a catarrhal duodenitis, which, in turn, is followed by pancreatic apoplexy. Inherited syphilis and infectious processes in the new-born are not infrequently associated with pancreatic hemorrhage. Exactly what the connection is can not, however, at present be definitely stated.

Morbid Anatomy.—The hemorrhage may be slight, consisting of punctate extravasations scattered through the organ; the

extravasations may be restricted to the interstitial tissue, or the blood may enter the gland spaces. In other cases the hemorrhagic infiltration may be uniform throughout a part of the gland, commonly the head; and in still other cases the whole gland may be involved. Occasionally, the hemorrhage involves the tissues around the organ, extending to the mesentery and retroperitoneal wall. The density of the organ will be partly dependent upon the age of the hemorrhage, its extent, and the condition of the tissues before the hemorrhage took place. The suffused tissues may be soft, as a result of liquefactive changes, or dense, in consequence of coagulation. The hemorrhages may have occurred at different times, as shown by the fact that in some areas old pigment may be found adjacent to, or in the vicinity of, recent hemorrhages. The source of the hemorrhage can rarely be located. In mild cases without extensive infiltration of the organ recovery unassociated with inflammation may occur. In the majority of cases, however, the lesion terminates in an acute inflammatory process. (See Acute Hemorrhagic Pancreatitis, below.)

Fatty infiltration of the pancreas is uncommon; it may be a part of general obesity, may result from retardation of the intra-abdominal circulation, or may be secondary to atrophic degenerative and fibroid processes occurring in the organ. *Calcareous infiltration* may accompany fat deposits or may follow hemorrhage or inflammation of the organ. The calcific material may be diffuse and scanty in amount, or may be collected in masses in some part of the organ.

Cloudy swelling and degenerative changes other than those already mentioned usually occur as part of similar changes in the liver and kidney, and are brought about by the same class of causes.

Atrophy of the pancreas in the large majority of cases is secondary to fibrosis involving the connective tissue of the organ, and constituting what is commonly described as chronic pancreatitis, which will be discussed with inflammations of the pancreas. After middle life the pancreas not infrequently participates in the atrophic changes involving many of the glandular viscera, muscles, and other organs.

Pancreatitis (*inflammation of the pancreas*) may be *acute* or *chronic*. The acute form is usually subdivided into the *acute hemorrhagic* and *acute suppurative*.

Acute hemorrhagic pancreatitis is usually a termination of the pancreatic apoplexy already described. In the earlier stage of the disease the morbid anatomy is that of pancreatic hemorrhage, and it is not improbable that what has been called pan-

creatic apoplexy is nothing but the initial stage of acute hemorrhagic pancreatitis. In addition to the enlargement of the pancreas and the diffused or punctate hemorrhages already described, there occur, in the organ, in the peripancreatic fat, and in the fat of the mesentery, omentum, and abdominal wall, areas of necrosis. (See Fat Necrosis, p. 252.)

If the patient survive, the inflammation may extend to the serous surface, giving rise to the presence of a blood-tinged fluid in the abdominal cavity, and to more or less fibrinous deposit on the surface of the serous membrane, particularly in the omental bursa. The extent of the hemorrhage and subsequent necrosis may involve a sufficient bulk of the pancreas to justify the term *pancreatic gangrene*. The gangrenous masses of pancreatic tissue may exfoliate and eventually reach the intestine, through which the masses may be discharged. Accompanying splenic enlargement is not infrequent, and thrombosis of the splenic vein may occur.

Acute suppurative pancreatitis assumes a number of forms, depending upon the source of infection and the presence or absence of previous disease of the organ. It may be a part of a general sepsis, in which case the multiple abscesses scattered through the organ are, of course, due to the deposit of infected emboli. In other cases the suppurative process is restricted to the pancreas, and may be secondary to the acute hemorrhagic or gangrenous pancreatitis already described. The lesion may be multiple; a single massive abscess or one of considerable size may result from confluence of many smaller abscesses. In the suppurative pancreatitis not preceded by the hemorrhagic lesion fat necrosis is inconspicuous or absent. The abscesses may penetrate the abdominal cavity, giving rise to general septic peritonitis; or they may be evacuated through the stomach or intestine. It is possible that a small purulent collection may inspissate and be partly healed in. The author has seen what he believes to have been such a condition. The suppurative process may be more or less chronic in point of time, and may end in a varying amount of fibroid change in the gland structure.

Chronic pancreatitis, *pancreatic sclerosis*, *indurative pancreatitis*, and *pancreatic fibrosis* are names given to a chronic process involving the pancreas and associated with the formation of more or less fibrous tissue.

Causes.—The lesion may be congenital or may be seen so soon after birth as to lead to the belief that it must have been in progress during intra-uterine life. Such fibroid changes are probably secondary to congenital syphilis. The cause of the

lesion in adult and middle life, after which time it becomes more conspicuous, is probably duodenal catarrh and subacute or chronic catarrhal inflammation of the pancreatic ducts.

Morbid Anatomy.—The amount of fibrous tissue may be such as distinctly to increase the size of the organ. In most cases, however, there is contraction, with atrophy of the glandular structures, and induration of the entire organ or only a part of the pancreas may be involved. The organ resists incision, and may be sufficiently fibroid to creak under the knife. It may be calcareous. The duct may be dilated or it may be normal. The

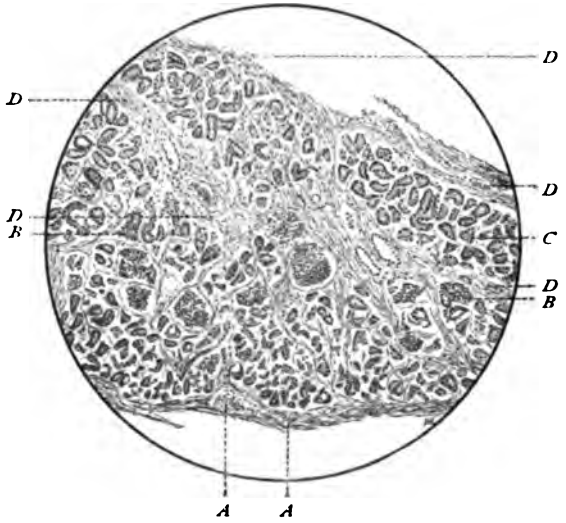


FIG. 313.—PANCREAS SHOWING INCREASE OF FIBROUS TISSUE. CHRONIC INTERSTITIAL PANCREATITIS.

A, A. Areas of hemorrhage. *B, B.* Immature gland cells (bodies of Langerhans). *C.* Gland acinus. *D, D, D, D, D.* Fibrous tissue; the areas of rhexis (*A, A*) are also in the fibrous tissue. (From a case of congenital syphilis.)

pancreas may be reduced to one-fourth or one-fifth of its normal weight. This is the lesion commonly observed in diabetes.

Tuberculosis and syphilis of the pancreas are rare infections, with the possible exception of the lesions induced by the congenital form of the latter.

Tumors of the Pancreas.—Cancer of the pancreas is the only neoplasm meriting special consideration. Carcinoma may be primary, which is usually the case; or it may be secondary, extension to the pancreas taking place from primary cancer involving the ampulla or biliary passage in the neighborhood of the

pancreas. The usual primary cancer of the pancreas is scirrhus. The cancer may be situated in any part of the organ, but is more frequently located in, or near, the head. The tumor varies in size, rarely attaining a diameter of from fifteen to twenty centimeters. By extension to contiguous tissues the duodenum and stomach are involved, and not infrequently metastases to the liver occur. Encephaloid cancer has been observed, and sarcoma, both primary and secondary, is occasionally seen. Aside from the cancer, however, other neoplasms are of extreme infrequency.

Cysts of the pancreas may occur at any age, and it is not improbable that those appearing early in childhood may be of congenital origin. Pancreatic cysts may be secondary to pancreatic inflammation, as is shown by the frequency with which cysts follow injury. Obstruction to the pancreatic duct by tumors and calculi, by parasites, or by stenosis due to chronic inflammation may give rise to a retention cyst of the organ, constituting what is known as a **pancreatic ranula** (*ranula pancreatica*). The cysts vary in size, the largest holding in the neighborhood of six liters. The contained fluid may be thin and watery, with a specific gravity of 1010; or it may be chocolate-colored and viscid, possessing a specific gravity between 1020 and 1030. In more recent cases the fluid may contain ferments that emulsify fats and digest starch. It is to be remembered that in old cysts pancreatic ferments may be absent. In very old cysts, particularly when hemorrhage has occurred in the cyst cavity, the resemblance to an aneurysm may be quite striking. The possibility of pure *cystoma* of the pancreas comparable to that described as occurring in the liver (see p. 360) must not be overlooked. A cystic disease of the pancreas resembling congenital cystic lesion in the kidney (see p. 634) is also possible.

Pancreatic calculi usually occur as round or oval, gray or grayish-white concretions, composed of lime salts, and attaining the size of a hazelnut; most commonly they are about the size of a grain of sand—from two to four millimeters in diameter. Sometimes the masses are putty-like. The number of calculi present may be a hundred or more, or only one stone may be found.

CHAPTER XIII.

DUCTLESS GLANDS.

THYROID GLAND.

Normal Histology.—The thyroid gland as found in the adult is composed of vesicles or follicles, round or oval, measuring from 35 μ to 125 μ in diameter. The epithelial wall of the follicle is formed by a single layer of columnar epithelial cells. These vary in height, and are placed directly upon a slightly condensed connective-tissue layer, which does not possess the usual characteristics of a basement membrane. The follicles contain a homogeneous colloid body, which gives slightly different reactions in different follicles and in different localities, constituting two forms of colloid, known as clear and dark colloid. There is an unusually rich supply of blood-vessels and lymphatics in the surrounding connective tissue. Sometimes lying within the thyroid, and at other times some distance away, are bodies resembling embryonic thyroid tissue, and composed of epithelium arranged in columns, but not forming distinct follicles, sacs, or tubes, and containing no characteristic colloid substance. That these bodies are not simply accessory, immature, or imperfectly formed thyroid elements would be indicated by the fact that their development is completed before that of the thyroid gland. Experimental evidence would seem to indicate that they may, however, assume some of the characteristics of the normal gland, especially when the latter has been removed or destroyed. These bodies are known as **parathyroids.**

The number of parathyroids varies; rarely, however, exceeding four. The fact that the removal of the thyroid gland induces changes resembling those seen after the removal of the parathyroids would further indicate that the function of the latter is accessory or compensatory to the former, and in man, as well as in lower animals, the removal of the thyroid may not be followed by symptoms, the remaining parathyroids assuming the functions of the body removed. In fetal life the thyroid possesses a duct that empties near the base of the tongue; remnants of this duct sometimes persist in postnatal life, and occasionally give rise to a cyst—**thyroglossal cyst.**

Malformation and Malposition.—Irregularities in the size of the lobes and in the quantity of tissue forming the isthmus and altered position of the parathyroids are not infrequent. Occasionally, masses of thyroid tissue are found lining the tract once followed by the duct, and distinct tumor-like accumulations may be present near the base of the tongue. In rare instances there may be great deficiency in the thyroid tissue, almost amounting to complete absence. Under such circumstances the parathyroids are usually conspicuous.

Anemia, Hyperemia, and Congestion of the Thyroids.—Of a purely local anemia involving the thyroid but little is known. Hyperemia is present in acute inflammatory processes, aside from which we have also an unusual vascular congestion, partly hyperemic and partly congestive, constituting the so-called vascular goiter. Congestion of the thyroid may be a part of the general venous distention occurring in cardiac diseases with failure to maintain the circulation. There is also evidence of its presence, as previously indicated, in vascular goiter.

Atrophy of the thyroid undoubtedly occurs, but the exact factors influential in establishing this condition are but poorly understood. It is not improbable that inflammatory and productive processes induce a sclerosis analogous to that seen in other secreting organs with which we are more familiar. In further support of this view is the well-known fact that occasionally cases of thyroid enlargement associated with exophthalmos, tremors, and rapid cardiac action show a progressive diminution in the size of the thyroid, which afterward remains small. The phenomena brought about by progressive atrophy of the thyroid are identical with those seen after the removal of the thyroid gland, the results of which have been studied in man, monkeys, and other animals.

The phenomena occurring in the patient are somewhat different when the thyroid gland has never been present—a condition constituting **sporadic cretinism, or congenital myxedema.**

The general disturbances of nutrition and arrest of development are usually not evident at birth, but commonly manifest themselves within the first year. The stunted growth, which particularly involves the long bones, associated with the thickening of the cranial bones, muscular weakness, intellectual deficiency, overgrowth of the subcutaneous tissue, which may be myxedematous, with yellowish, dry skin, brittle, scanty hair, protruding lips, thickened tongue, and more or less salivation, comprise the clinical and pathologic picture. Cretins rarely attain a height of five feet, and sometimes do not exceed three feet.

Closely resembling the condition just mentioned are the tissue and nutritive changes resulting from destructive processes attacking the thyroid gland. The destruction may be due to the occurrence of cysts, to fibrous deposits, or to tumor invasion, and constitutes a part of the anatomic basis of the disease called **myxedema.** Myxedema usually occurs later in life; ninety per cent. of the cases are in women. The tissue changes resemble those seen in sporadic cretinism, except that the further development of the body, which may be completed, considerably alters the picture. There is a more conspicuous thickening of the subcutaneous tissues, with dry, rough, or scaly skin, broad and flattened digits, thick and overhanging lips, mental dullness, and evident poor nutrition of the hair, as already mentioned as present in cretinism. The mucous membranes and submucous tissues show changes resembling those noted in the skin. There is submucous tumefaction, particularly marked in the lips, mouth, and tongue, and sometimes in the palate. The teeth become carious, and sometimes fall out.

Cachexia Strumipriva (Postoperative Myxedema).—As a result of the clinical observations of Kocher, Raverdin, and others, and the experimental research of Horsley, Edmunds and Vassale, and Generali, it has been found that total ablation of the thyroid is followed by phenomena resembling those seen in cretinism and myxedema. The occurrence of this condition is dependent upon the more or less complete removal of the thyroid and parathyroids; the resulting disease is evidently due to the absence of thyroid function, as indicated by the fact that grafting of thyroids into thyroidectomized animals leads to the disappearance of the symptoms, and, further, that the administration of thyroid extract in this condition, as well as in cretinism and myxedema, arrests, or at least greatly modifies, the diseases in question. Apparently, these conditions are due to thyroid inactivity, insufficiency, or absence.

Hypertrophy of the thyroid will be considered with tumors.

Infiltrations and Degenerations.—Aside from the occasional presence of calcareous material in the thyroid gland, as well as hyaline substances and bodies resembling lardaceous material, nothing is known of the special forms of infiltration and degeneration occurring in this organ. Degenerative changes are constantly present in the epithelium lining the follicles; their significance, however, is not at present appreciated.

Of **strumitis, or inflammation of the thyroid gland,** but little is known, except in the acute suppurative form due to infection through the blood stream, by wounds, etc.

Tuberculosis occurs as a primary miliary tuberculosis, and also occasionally as a chronic localized caseous lesion.

Aside from **gumma,** but little is known of syphilitic lesions in the thyroid gland. The author has had an opportunity to observe one case in which a temporary thyroid enlargement occurred with the outbreak of secondary symptoms. The cause and significance of such a condition is, of course, undetermined. A gumma is usually solitary, rarely possessing any peculiarity in its structure.

Goiter.—The terms goiter, bronchocele, thyrocele, and struma have been indiscriminately applied to all enlargements of the thyroid gland, and the condition, therefore, includes tumors of various kinds and cysts, as well as true thyroid hyperplasia.

The enlargement may be limited to one or both lobes, associated with involvement of the isthmus; or, in rare instances, the isthmus alone may be involved. Goiters are said to be *hyperplastic*, *cystic*, or *malignant*. Certainly, some of the cysts should be considered with the neoplasms, and the indefinite term malignant should be supplanted by sarcoma and carcinoma, and hence such conditions should be described with tumors of the gland. By some the so-called *vascular goiters* are included with those believed to be hyperplastic in origin. When the thyroid enlargement is due to active growth of the gland structure, with or without a proportionate increase of the connective tissue, the condition has been termed **parenchymatous goiter.** When proliferative changes are conspicuous in the connective tissue of the gland, the term **fibrous goiter** is applied. . When the goiter is associated with unusual enlargements of the blood-vessels,—and it is usually the more superficial veins that show this change,—the term **vascular goiter** is applied. The increased vascularity may be recognized in the gland stroma, and may cause pulsation; it is not infrequently conspicuous in that form of goiter that constitutes a part of the clinical picture of **Grave's disease—exophthalmic goiter.** Clinically, Grave's disease is marked by the occurrence of goiter, exophthalmos, tachycardia, and trembling. One or more of the cardinal symptoms may be absent. The enlargement of the thyroid may be but slightly marked, and in other cases the gland shows considerable increase in size. It is commonly uniform. Histologically, there is usually evident hyperplasia, as shown by the enlarged vesicles, tall epithelium instead of the low epithelium, and the occasional occurrence of papillary ingrowths. The alterations seen in the gland resemble those observed in residual follicles after partial ablation, and possibly justify the use of the term *hypertrophic.* It is com-

monly held that the symptoms as well as the glandular changes are entirely unlike those seen in myxedema, and that the latter condition is due to a want of thyroid function, and the former to overactivity. This view is further supported by the fact that the administration of thyroid extract induces symptoms resembling those of Grave's disease. The fact, however, that exophthalmos has never been experimentally induced by the administration of thyroid extract militates against this view. That the symptoms are partly due to hypersecretion is further indicated by the fact that temporary relief follows the partial ablation of thyroid tissue. It has been held that not only is the secretory activity of the gland greater than the normal, but that there is at the same time the production of abnormal substances or some particular body out of proportion to other or associated elements. The belief in the exclusively nervous origin of Grave's disease does not seem to be supported by sufficient evidence, although the frequent presence of the disease in women belonging to families in which occur chorea, hysteria, or epilepsy, and the fact that the disease may rapidly succeed emotional disturbances, offers certain support to the theory of its nervous origin.

Tumors of the Thyroid Gland.—The uniform enlargement of the gland seen in exophthalmic goiter has been referred to occasionally as adenomatous goiter. The application of the term in this way is probably incorrect. That condition called **adenoma of the thyroid,** like adenoma of other glands, should be restricted to the formation of new gland tissue that does not constitute a part of the normal gland within which it may be located. Occasionally, adenomata are cystic, and in some cases the walls of the cysts show papillary ingrowths, thus constituting *papillary* or *proliferous cyst adenomata* of the thyroid.

Carcinoma of the thyroid occurs as a primary affection, which is usually encephaloid in character. Secondary invasion of the thyroid is infrequent. Of the adult connective-tissue tumors fibroma, chondroma, and osteoma are most frequent. Sarcomatous involvement of the thyroid commonly gives rise to an extremely soft, semifluctuating tumor, which may be mistaken for a cyst; commonly, the rapidity of its growth is striking.

The *cysts* seen in the thyroid may consist of numerous cavities, some of which may be large, and are the result of distention, either alone or with coalescence of the normal gland follicles. Rarely a cyst may be unilocular; in the majority of cases it is multilocular. The growth is usually slow; the cyst contains albumin, occasionally a trace of oil, and sometimes

colloid material. Cystomata of the thyroid have been described. Parasitic cysts occur, but are infrequent.

SUPRARENALS.

Malformation and Malposition.—The suprarenal bodies may be absent or hyperplastic. Accessory bodies may occur. The supernumerary bodies may be near their normal position, or they may be in the capsule or cortex of the kidney, and, less frequently, a considerable distance from their normal site, as in the pelvis or scrotum.

Atrophy of the suprarenals may be associated with fibroid change, may result from pressure, is not infrequently marked in old age, and may be secondary to inflammatory processes occurring in the vicinity of the gland. A simple atrophy has been described in which it is stated that the organs are no larger than peas.

Infiltrations.—A gland otherwise normal may show a small amount of adventitious *pigmentation*, particularly in old age. As a rule, the pigment deposit does not involve the whole organ, but is restricted to one or more layers of the cortex, extending, to a certain degree, into the adjacent medulla. *Lardaceous disease* may involve the blood-vessels and, to a very limited extent, the connective tissue of the organ; the iodin and microchemic reactions (p. 230) are best seen in the cortex. *Calcareous infiltration* occurs in chronic infections that involve the gland, and is not infrequently present without any evidence of inflammation or tuberculosis.

Degenerations. — *Parenchymatous* and *fatty degenerations* have been described, but little is known of their etiology or course.

Hemorrhage into and around the gland may result from trauma and marked congestion. Rarely the extravasation may be diffuse, and still less frequently a distinct hematoma may be formed.

Inflammation of the suprarenal may assume an acute or chronic form. Of the acute form but little is known, with the exception of an occasional suppurative lesion secondary to infection by means of the blood or involvement as a result of the extension of infection from adjacent suppurative processes. In the chronic form induration of the gland occurs, brought about by the production of new fibrous tissue; the lesion is, therefore, comparable to the chronic inflammations that involve other glands.

Syphilis of the suprarenals may be manifested by the pres-

ence of gummata, which may be single or multiple; occasionally, a fibrosis of the organ occurs attributable to syphilis.

Tuberculosis of the suprarenals is probably the most frequent disease to which the organ is liable. In general miliary tuberculosis the adrenal, in common with other organs of the body, is usually affected. The most frequent lesion of the adrenal, however, is the chronic fibrocaseous form of tuberculosis. The condition may be primary, but in a large percentage of cases is secondary. The tuberculous deposit usually begins in the medullary portion as scattered tubercles, which, by coalescing, convert the organ into a more or less caseous mass with a notable increase in the fibrous tissue or, not infrequently, extensive calcareous infiltration. The tuberculosis may extend from the gland proper to the surrounding tissues.

Tumors of the Suprarenals.—The most frequent neoplasm is *adenoma*. Adenomata may be more or less diffuse, consisting of irregularly outlined nodules in the gland tissue, or the tumor may be sharply circumscribed. Virchow described a form of adenoma that he termed *struma lipomatosa suprarenalis*. Such tumors simulate in structure the cortex of the organ. *Cancer* of the suprarenal may be primary or secondary. Adult connective-tissue neoplasms are extremely rare. *Sarcoma*, both primary and secondary, occurs, but is far less frequent than cancer. The *cysts* observed in the suprarenals may result from hemorrhage or degenerative changes in adenomata. Hydatid cysts are occasionally met with.

Addison's Disease.—Associated with tuberculosis, atrophy, simple or inflammatory, neoplasms, or hemorrhage into the suprarenals, there occurs a series of clinical phenomena to which has been applied the name Addison's disease. Tuberculosis of the suprarenal bodies is the lesion most frequently found (about 75 per cent. of the cases). In addition to the changes observed in the adrenal glands, there occurs a bronzing of the skin, due to a deposit of pigment in the Malpighian layer. The cutaneous pigmentation is not uniformly distributed, but is usually most marked on the exposed parts. A similar coloration of the buccal mucosa may be present, and pigmented areas occur on the tongue. The nervous, muscular, and cardiovascular phenomena are not accounted for by the morbid anatomy. The disease is said to occur without demonstrable lesion of the suprarenal bodies. It is usually held that the phenomena are caused by a suprarenal inadequacy.

CHAPTER XIV.

THE VOLUNTARY MUSCLES.

A **normal voluntary muscle** is formed of *fibers* held together by the *endomysium;* these, collected in larger groups, are surrounded by the *perimysium*, and in many localities the muscle is partly retained within a distinct sheath called the *epimysium*. The fibers forming the muscle vary in length, rarely exceeding, however, from 3 to 5 cm., and measuring from 10 μ to 50 μ in width. Each muscle-fiber is composed of a contractile substance with peripherally placed nuclei and surrounded by a sheath called the *sarcolemma*. The various views with regard to the ultimate structure of the fibers will be found in works on histology, and do not especially interest the pathologist.

Many **malformations** and slight alterations in the origin, course, and insertion of muscles occur. These, however, are of anatomic rather than of pathologic interest.

Atrophy of muscle occurs under a number of conditions. Persistent pressure rapidly leads to disappearance of the contractile substance, with more or less substitution of fibrous tissue. A muscle not performing any function usually shows progressive wasting, constituting atrophy from disuse; such atrophies are intensified by associated pressure, as is seen when a fractured bone demands absolute rest and, at the same time, is subjected to the pressure of retentive dressings. Fixation of a joint (ankylosis), section of a tendon or muscle, and causes removing the force that induces normal muscular tension may also bring about atrophy. Interference with innervation, particularly the removal of motor stimulation as the result of diseases of the motor neurons or axons, may also bring about atrophy. Such atrophies are typified in the spinal and bulbar lesions of the central nervous system. As the disease usually begins in certain muscles, depending, of course, upon the location of the central lesion, and gradually progresses with the changes in the central nervous system, the term **progressive spinal amyotrophy** has been applied. (See Diseases of the Nervous System.) In the disease called *poliomyelitis*, particularly frequent in childhood, there occurs an acute inflammatory lesion involving the motor cells in the an-

terior horns of the spinal cord, with subsequent degenerative changes in these structures; as a result of the lesion in the cord, paralysis, followed by atrophic processes, occur in the muscles controlled by the affected neurons, constituting a condition called *infantile paralysis.* (See Diseases of the Nervous System.) In other cases the atrophic process is unassociated with recognizable lesions of the central nervous system or peripheral nerve; in such cases the wasting is presumed to be essentially a disease of the muscle, and the term **primary myopathy** is applied. Certain of these atrophies closely resemble the progressive spinal form, and they have been grouped under the head of **progressive muscular dystrophy.**

Pseudohypertrophic muscular paralysis (*myosclerosis*) is a disease most frequent in male children, although occasionally it is seen in girls; two or more members of the same family may be attacked. Usually, the first indications of the disease are observed in the muscles of the calves, which show considerable enlargement, and may or may not be associated with corresponding increase in the volume of the anterior tibials. The marked enlargement commonly occurs in the gluteus maximus, and usually, although to a lesser degree, in the extensors of the thigh. The prominence of these muscles gives the appearance of hypertrophy, and hence the name. As the increase in size is associated with deficient contractile power (lessened function), the term pseudohypertrophy is appropriately applied. Associated with the increase in the size of the muscles indicated, others may show an early wasting—as, for example, the flexors of the knee and thigh. In the upper extremities the deltoid, supraspinatus, infraspinatus, and triceps are enlarged, while the biceps may be atrophied. Histologically, during the stage of enlargement the muscle-fibers may show but slight alteration; there is, however, an enormous increase in the amount of fat between the fibers, to the presence of which the appearance of hypertrophy is due. (See Fig. 314, also Fig. 175, p. 227.) As a rule, the transverse measurement of the muscle-fiber is diminished, although occasionally fibers of unusual size are to be noticed. Later, there is a marked increase in the amount of fibrous tissue without corresponding continued overgrowth of the fat. The muscle-fibers become thin and irregular. The striation, at first nearly normal, rapidly grows less conspicuous, and eventually disappears. Fat has been observed within the sarcolemma, which, associated with the granular changes in the fibers, would indicate that the process is essentially a degeneration. The alterations in the contractile substance are not uniform and do not implicate at one time all the fibers in a given muscle, nor

are all the fibers in one area simultaneously involved; it is, therefore, patchy, diffused, or irregular in distribution. Late in the process, when the false hypertrophy has disappeared, the fragmentation, degeneration, and absorption of the true sarcous elements are most marked.

A form of muscular atrophy occurs unassociated with the preliminary stage of pseudohypertrophy, and appearing more frequently in young adults than in children. Two types of the lesion have been described—(1) one by Erb and (2) one by Landouzy and Déjerine. As to the relation of the two forms, opinions differ; some maintaining their identity, and others holding that they are distinct processes. While to a certain extent different muscular systems are involved, the lesions in the affected

FIG. 314.—SECTION TAKEN FROM THE GASTROCNEMIUS MUSCLE OF A CHILD SUFFERING FROM PSEUDOHYPERTROPHIC MUSCULAR PARALYSIS, FIXED IN FLEMMING'S SOLUTION, AND STAINED WITH HEMATOXYLIN AND EOSIN. (Specimen lent by Dr. Harris.)

a. Muscle-fibers. *b*. Fibrous and fatty tissue. *c*. Blood-vessel, the lumen of which has been occluded by fibrous tissue. The disarrangement of the muscle-fibers and the increase in the fibrous and fatty tissue are well shown. (Queen obj., ⅔-in.; oc., B.)

muscles are not unlike. In the form described by Landouzy and Déjerine the wasting begins in the face, and next involves the muscles of the shoulders and arms. This peculiarity has led to its being called the *facioscapulohumeral* type. In that form of muscular dystrophy described by Erb the face is not affected. The pectoral muscles, trapezius, latissimus dorsi, biceps, triceps, brachialis anticus, and supinator longus, and later the muscles of the lower extremity, are involved. On section, the muscles may have lost their normal color, and are largely composed of fibrous and fatty tissue. The remaining muscle-fibers are small; at first striation is retained, but later it disappears. It is usually held that the initial changes are in the muscle-fibers and that the increase of connective tissue is secondary. In many

cases, however, the reverse seems to be true. No secondary lesion in the cord or ganglia has been recognized.

FIG. 315.—PROGRESSIVE MUSCULAR DYSTROPHY, ERB TYPE. (From "Pennsylvania Medical Journal," March, 1898; report by Dr. Theodore Diller, to whom the author is indebted for the illustration.)

The atrophy of the muscles forming the shoulder girdle, the pelvic girdle, and the arms and thighs is well shown. Notice the marked lordosis. The muscles of the forearm and calves are not involved.

True hypertrophy of muscle is usually dependent upon an increased demand for work accompanied by sufficient nutrition.

It is most highly developed in athletes, where systematic training has brought the muscles to the highest degree of functional power. Occasionally, the hypertrophy may be restricted to certain groups of muscles, and may, in these cases, be dependent upon some special work thrown upon them, as is seen in the muscles of toe-dancers and in artisans in whom certain groups of muscles are brought particularly into play. A certain amount of muscular hypertrophy is also seen in Thomsen's Disease (*congenital myotonia*).

A typical example of hypertrophy resulting from increased work is seen in valvular disease of the heart. (See p. 512.)

Of the **infiltrations** occurring to muscles, *pigmentation* is deserving of mention as being frequently associated with various atrophic processes. The infiltration is also seen in old inflammatory areas and in the neighborhood of chronic infectious processes. Occasionally, acute inflammatory lesions of the muscles may be followed by the deposit of considerable calcareous material. *Amyloid infiltration* is rare; it is occasionally observed in the neighborhood of inflammatory processes, and at times is seen independent of existing inflammation. The muscles of the tongue and larynx are said to show the changes most frequently. The deposit is between the fibers.

Degenerations.—Of the various degenerative changes in muscles, *cloudy swelling* and *fatty degeneration* are most common. The alterations seen in the fibers are not different from those already described in the heart muscle. (See pp. 241, 242, and 493.) In edema *vacuolization* or *hydropic degeneration* of the fibers occurs. It is usually manifested by the appearance of vacuoles within the fibers. These vacuoles are sometimes numerous and small, and in other instances they are large and single. (See pp. 240 and 244.) Distinct separation of the contractile substances (fragmentation) frequently follows degenerative changes, and an interstitial fibrosis is also occasionally present. Hyaline degeneration (p. 246), accompanied or preceded by coagulation necrosis (p. 250) of the muscle-fibers, is observed in the course of infective diseases—conspicuous among which may be mentioned typhoid fever, in which disease the abdominal muscles most frequently show the change.

Myositis.—*Inflammation of muscle* is usually dependent upon the extension of irritation or infection from adjacent structures, and is therefore most frequently secondary. In other instances it represents an infective process occurring in the muscles and is secondary to the deposit of bacteria from the circulation; and in still other cases it may be dependent upon trauma, upon inva-

sion of the muscles by parasites, or it may be a manifestation of actinomycosis or syphilis.

Acute polymyositis is an inflammatory affection of the muscles closely resembling trichinosis, and hence sometimes called *pseudotrichinosis*. Little is known of the cause of the condition. Its resemblance to trichinosis has led some authors to conclude that it may be dependent upon some microbic or parasitic invasion; other writers are inclined to believe that the cause is a toxin or other poison acting upon the muscles through the blood.

Morbid Anatomy.—Almost any muscle may be affected. The muscle is hyperemic, edematous, soft, and usually shows minute hemorrhages irregularly disseminated throughout. Histologically, the muscle-fibers are at first swollen and granular, with imperfectly marked striation; later, they are waxy and hyaline. The interstitial tissue commonly shows an unusual richness in cells, with areas of hemorrhagic infiltration.

Suppurative Myositis.—The acute pyogenic infections involving the muscle induce lesions showing no important differences from similar processes occurring elsewhere. The purulent process is accompanied by the usual migration of leukocytes, liquefaction of the connective tissues, the progressive degeneration, coagulation, and eventually necrosis of the muscle. The condition is usually dependent upon the invasion of the muscle by cocci, notably streptococci and the staphylococci. (See Abscess, p. 290.)

Chronic myositis associated with syphilis has been described. The same lesion also occurs in other conditions. The muscles are pale in most cases, although occasionally they are pigmented. There is an increase in the fibrous tissue, rendering them tougher than normal. The muscle-fibers usually show, sooner or later, granular changes and more or less atrophy. Disappearance of striation occurs, although occasionally the muscles may evince considerable atrophy, with persistence of the striæ.

Under the title **ossifying myositis** has been described an affection the inflammatory character of which has been indisputably established. The inflammation is associated with the appearance of calcareous deposits between, in, or near the muscles. The fact that the muscle-fibers show but little alteration, even late in the process, would indicate that the disease essentially involves the connective tissues. In some cases the bony deposit follows trauma; in other cases a history of trauma is absent. There is usually proliferation of the connective tissue of the muscle, which progresses to the formation of bone, very much as

is observed in the proliferative process affecting the periosteum. As the process is not restricted to the muscle, but occurs also in the fasciæ and tendons, all sorts of irregular osseous or osteoid collections may occur. The disease pursues a chronic course, usually beginning in the muscles of the neck or back, to which it may remain restricted. Later, it may progress and involve all the muscles of the trunk, with ankylosis of joints, rendering the body practically rigid. The bony collections are irregular, consisting of flakes and spicules, which later may show more or less coalescence.

Chronic Infectious Diseases of the Muscles.—Of all the tissues in the body, the muscle seems strangely resistant to *tuberculosis*. Even in widely disseminated acute miliary tuberculosis the muscle usually escapes. In chronic tubercular lesions invasion of the muscle by contiguity occasionally occurs. Aside from the chronic interstitial myositis believed to be syphilitic, *gummata* are occasionally seen in the muscle ; they are, however, infrequent. Glanders and actinomycosis occasionally invade the muscles.

Of the **tumors** occurring in the muscle, *chondromata* and *osteomata* are probably the most frequent, although *fibromata* are occasionally observed. Lipomatous collections between the muscles sometimes appear actually to invade the muscle. True muscle tumors are extremely rare. The most frequent primary tumor of muscle is *sarcoma*.

Parasites.—Trichinæ (p. 198), cysticercus cellulosæ (p. 204), and hydatids (pp. 206 to 209) invade the muscles.

CHAPTER XV.

BONES AND JOINTS.

THE BONES.

Normal Structure.—Histologically, bone consists of a modified form of connective tissue presenting certain structural peculiarities in different bones and in different parts of the same bone. The long bones, except at the articular ends, are covered by a membrane called the *periosteum*. This structure is a dense connective-tissue membrane composed of two distinct layers. The outer layer affords attachment for the aponeuroses, tendons, ligaments, fasciæ, etc., with which it is practically continuous. It is comparatively rich in blood-vessels, some of which pass to the underlying layer and afford additional nutrition to the adjacent bone. As a result of its intimate association with the surrounding tissues, this layer of the periosteum is more or less liable to the diseases, particularly the chronic infective processes, involving the adjacent structures. It is intimately connected with the underlying or genetic layer, from which it can not always be easily differentiated, the two forming a fairly uniform membrane. The outer layer is composed of dense fibrous tissue; the inner layer is richer in elastic tissue, and immediately adjacent to the superficial layer of bone it contains, in varying numbers, osteoblastic elements, through the activity of which the circumferential growth of the bone is secured. The degree of adhesion between the inner layer and the bone proper varies. Besides the somewhat loose cellular attachment, the genetic layer is further secured in many localities by the presence of certain fibers that penetrate the compact portion of the bone, and also by the vascular communication between the bone and the periosteum, through which, in part, the nutrition of both is maintained.

Immediately adjacent to the periosteum is the *compact portion* of the bone, while still deeper the supporting osseous structure assumes a spongy consistence, constituting the *spongy layer*. The quantity of compact tissue, as compared with the spongy, varies in different bones and is not uniform for all parts of the same bone. Thus, in the long bones there is a relatively thick, compact layer in the shaft, while the extremities are composed for

the most part of spongy tissue covered by a thin shell of compact bone. The circulation of fluids within the compact portion of the bone is secured through the presence of two systems of channels—one of these is called Volkmann's canals and the other the Haversian canals. The latter differ from the former in the fact that each canal constitutes the center of a lamellar system. Around this central canal are arranged successive plates of osseous ground-substance, constituting the Haversian lamellæ. Between the latter are incomplete or partial lamellæ, called the interstitial lamellæ, while at the periphery, immediately under the periosteum, are the periosteal or outer circumferential lamellæ. Within the various lamellæ already mentioned are smaller canals, called the lacunæ. The compact layer of the bone, projected inward toward the medulla, divides the inner area into small spaces, resembling the open spaces found in a sponge, and hence this portion of the bone is called the spongy layer. In the meshes of this sponge-like tissue is held the bone-marrow, which further occupies the central canal or cavity of bone.

Bone-marrow.—Macroscopically, two kinds of marrow are recognized: (1) A *red marrow*, composed of a connective-tissue reticulum holding in its meshes certain cellular elements. (See Figs. 315 and 316.) Conspicuous among the cells of the marrow are the uninucleated and multinucleated giant cells. Some of these cells attain a diameter three or four times that of the finely granular oxyphile leukocyte, while cells tinctorially and structurally identical, but much smaller in size, are to be recognized as probably miniature myeloplaxes. Leukocytes are present in varying stages of development; if it is assumed that the white blood-cells are different throughout their life history, then it must be stated that all kinds of leukocytes are found in the bone-marrow. (See Table of Leukocytes, pp. 430 and 431.) The bone-marrow also contains a cell presumed to be the parent of the erythrocyte—called the *erythroblast*. The latter is nucleated; the nucleus possesses the usual affinity for basic dyes, while the cell cytoplasm gives, to a varying extent, the tinctorial reaction of protoplasm containing hemoglobin. The amount of fat present in this type of marrow varies, but it is usually not abundant.

The (2) *yellow marrow* is composed largely of fat, and contains but few of the special cellular elements just described, and even these are absent in many localities.

The nutrition of the bone is secured through an abundant blood supply entering by means of the vascular twigs in the periosteum, to which reference has already been made, as well as by

special nutritive branches. The vascular twigs from the periosteum pass through the Haversian and Volkmann's canals, communicating with branches from the bone-marrow having their origin in the nutritive vessels passing through the compact portion of the bone directly to the marrow tissue. During the earlier periods of osseous growth a high degree of vascularity is necessary for the general nutrition of the bone as well as for its enlargement circumferentially and axially. In long bones

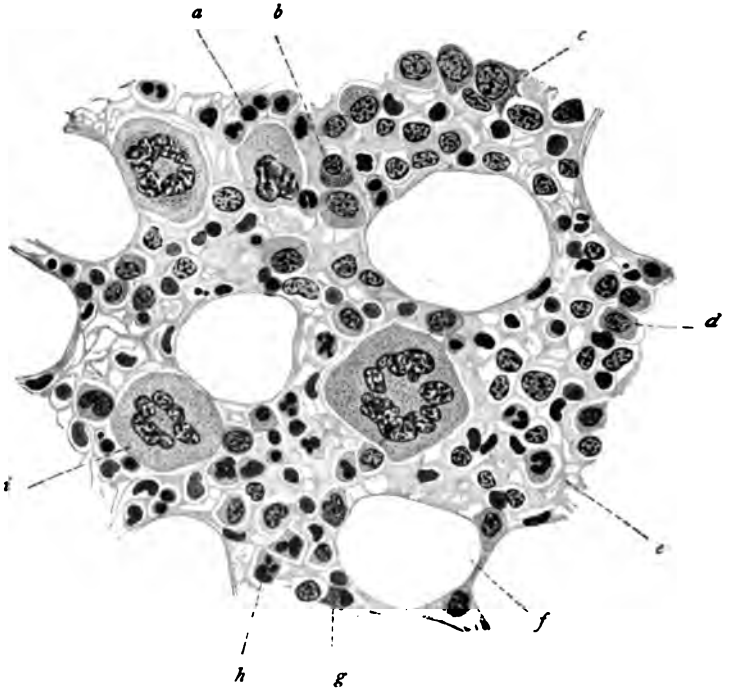


FIG. 316.—SECTION OF BONE-MARROW OF RABBIT, SHOWING THE DELICATE CONNECTIVE-TISSUE RETICULUM CONTAINING THE DIFFERENT ELEMENTS OF THE MARROW. ×400. —(*Schafer.*)

a, *h*. Hematoblasts. *b*, *g*. Eosinophilous cells (granule cells). *c*, *d*. Marrow cells (plasma cells). *e*. Connective-tissue reticulum. *f*. Fat space. *i*. Giant cell.

possessing epiphyses there is usually an abundant vascular network between these structures and the shaft, properly so called. At this line of junction the veins afford communication between the overlying tissues and the bone-marrow, and hence infective or inflammatory processes attacking these special areas are extremely prone to involve, when arising externally, the medulla; the reverse is also true.

For a description of the process by which bone is developed the student is referred to standard text-books on histology and embryology. There is, however, one element deserving of special consideration, by reason of the fact that it has important bearings on pathologic processes affecting the bones, and, in the latter form, usually closely resembles the normal process. The condition to which reference is made is called **osseous resorption.** Bone is absorbed through the intervention of giant cells; these cells apply themselves directly to the calcified matrix, within which they excavate small cavities, called *Howship's lacunæ*. The giant cells are called *osteoclasts*. Conclusive evidence as to the method by which they bring about the excavation in the calcified matrix is still wanting. It is reasonable, however, to assume that the cell secretes a material that liquefies and renders absorbable the dense structure, making the process closely allied to certain forms of phagocytosis. In growing

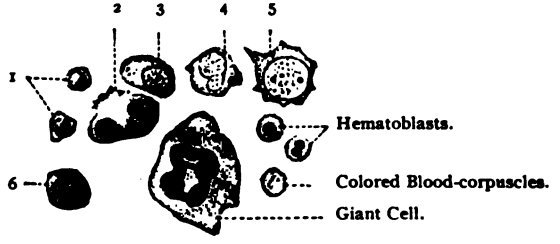


FIG. 317.—ELEMENTS OF HUMAN BONE-MARROW. ×600.
1 to 5. Various forms of bone-cells. 6. Eosinophilous cell.—(*Stöhr.*)

bone, while the osteoclasts are gradually leading to osseous absorption in the interior, the exterior of the bone is receiving additional bone, laid down by cells already mentioned as present in the genetic layer of the periosteum, and called *osteoblasts*. This laying-down of bone from the periosteum is called **osseous apposition.**

Malformation of Bone.—In the osseous skeleton many perversions of development occur. These are usually manifested through arrests that may themselves be due to recognizable diseases of the blood-vessels or may arise without a demonstrable cause. As the larger part of the osseous skeleton is preceded by a stage of cartilage, any defect in the laying-down of this primary enchondral matrix (**achondroplasia**) becomes manifest in the later growth and development of the bone. Aside from these defects in the initial process of osseous growth, there is to be

recognized, later, certain malformations depending upon failure in the extent of growth; or it would be better to say the formation of the bone is not completed. Thus, arches may fail to coalesce, as is observed in the superior maxilla, where developmental arrest gives rise to harelip (see p. 647), cleft palate, etc.; or in the chest, resulting in the formation of a fissure that may extend the entire length of the sternum. A posterior fissural deficiency is sometimes present in the spinal column, the lamina of the vertebræ having failed to complete the arch that normally forms the posterior wall of the spinal canal, giving rise to the presence of a fissure, constituting a condition known as *spina bifida*. (See Malformation of the Central Nervous System.)

Agenesis may be restricted to one bone, or even to a part of the bone, or it may be more extensive, involving the osseous structures of a large area. Sometimes the defective development is remarkably uniform, all the bones of the skeleton being influenced to approximately the same degree, giving rise to the typically symmetric and accurately miniature individual called the dwarf—**microsomia, nanosomia.** In other cases the arrest in development may be restricted to certain areas or to certain bones, leading to asymmetry, one limb or one part of the pelvis or one side of the chest showing a development that approximates the normal and is far in excess of that attained by the opposite side.

Of the ultimate cause of these conditions little is known. Local arrests may depend upon morbid processes influencing the nutritive organs during developmental stages; prominent among the causes acting in this way may be mentioned rickets and syphilis. The deformities indicated are commonly attributed to inheritance, diseases of the thyroid gland, imperfect osteogenesis, etc.; it must be evident that such explanations are insufficient and unsatisfactory.

It is equally difficult to explain the remarkable overgrowth of bone occasionally observed. The fact that osseous overgrowth is sometimes associated with diseases of the hypophysis cerebri offers but little aid in our effort to solve this obscure problem. Knowing nothing of the functions of the hypophysis, it is quite impossible, for the present at least, to infer the actual relation existing between morbid processes in this organ and the tissue overgrowth involving the bones and other tissues. In acromegaly a more or less uniform enlargement of many of the bones of the skeleton occurs. There is true increase in length and circumferential enlargement due to the deposit of osseous matter in the subperiosteal layers, either alone or associated with osteophytic excrescences.

Hemorrhage under the periosteum, giving rise to more or less detachment of the membrane, occurs in scurvy, and other blood dyscrasias, and in cephalhematoma; the last-named condition results from the trauma of labor. The extent of the hemorrhage largely depends upon its cause, and upon the resistance of the individual. In marked cases of infantile scurvy the periosteum may be dissected loose from the bone over a large area, so that the shaft of the femur, for example, may show only a periosteal attachment at each end, the intermediate area having been detached by the blood-clot. The immediate sequences and ultimate results of such hemorrhage largely depend upon the presence or absence of infection. When bacteria or bacterial products are excluded, death of the bone is not so likely to occur, more or less absorption, and, later, organization of the effused blood taking place. In the presence of infection, suppuration with extensive necrosis, septicemia, pyemia, and death are the usual results.

Periostitis.—Inflammation of the periosteum may be *acute* or *chronic*, *simple* or *noninfective* and unassociated with the presence of bacteria, or it may be *suppurative*.

Acute Simple Periostitis.—Under this head must be grouped the more or less trifling inflammatory and reparative changes resulting from bruises, knocks, and injuries of the periosteum, and unattended by infection.

Under such circumstances the periosteum is swollen, and may be separated from the underlying bone by subperiosteal hemorrhage. The density of the periosteum militates against the occurrence of marked redness and injection, although they may be present. Quickly following the injury and hemorrhage, absorption of the blood begins; this is accompanied by a varying amount of proliferation of the connective tissue, including the genetic layer of the periosteum, with more or less leukocytic infiltration. The extruded blood is largely removed through the agency of the phagocytes, and the resulting cellular accumulation passes on to the formation of cicatricial tissue, which may become calcified or may be, by reason of the osteoblastic elements present in the periosteum, in part converted into bone.

Acute suppurative periostitis commonly follows trauma with infection, although mycotic lodgment in the periosteal structures may occasionally occur without any antecedent injury sufficiently important to be recalled by the patient at the time when symptoms first manifest themselves. It may be secondary to an osteomyelitis.

The organisms most frequently associated with this condition

are the pyogenic cocci, the colon bacillus, the pneumococcus, occasionally the typhoid bacillus, and less frequently other microbes. The bacteria may reach the point of colonization by means of the blood, as their occasional presence in the circulation is now conceded to be a possibility. In other cases the infection may be direct, as by trauma. The periostitis just described may be converted into the suppurative form by the lodgment of bacteria at the newly evolved point of least resistance. When a preinfective stage is present, the changes are those already described as present in the acute simple form.

With the inception of infection, coagulation necrosis and the filling of the area with finely granular oxyphile leukocytes occur, converting the inflammatory exudate into pus. This always tends to extend, usually involving, to a certain extent, the underlying bone, which is further influenced by the fact that the nutrition to its periphery is cut off as a result of the separation of the periosteum. The density of the fibro-elastic membrane does not favor the easy escape of the infective material, and hence the latter is likely to detach the periosteum for some distance beyond the original area of involvement. The rapidity and the extent of the process depend upon the susceptibility of the individual and upon the activity of the infective agent. Thus, in debilitated patients trifling initial lesions may be followed by the gravest consequences, and when lessened protective powers are associated with virulent infection, extensive necrotic processes may ensue. Occasionally, the suppuration may be circumscribed, the bacteria may be destroyed, and an area of healed-in suppuration is formed. In other instances perforation of the periosteum takes place and a paraosteal suppuration follows. The extension of the infective processes may be rapid, often surrounding the joint and inducing a periarticular abscess. In other instances it may lead to separation of the epiphysis, and even penetrate the joint, or from the juxta-epiphyseal line may involve the medulla of the bone, inducing thereby a more or less typical osteomyelitis. Occasionally, the infective process is further complicated by the presence of hemorrhage, and to this form has been given the name **hemorrhagic periostitis.**

A chronic inflammatory process occurs in the periosteum, and has been called **fibrous periostitis.** It is at times to be regarded as a consequence of the simple acute periosteal inflammation; in other cases syphilis appears to be the cause; and in still other instances it is secondary to inflammatory and infectious diseases primarily in adjacent tissues. It is essentially chronic from the beginning, lasting for years, is not usually associated

with marked symptoms or prominent tissue changes, and but rarely is transformed into a more grave type of periosteal disease.

The periosteum is thickened, extremely dense, and firmly attached to the underlying bone. Calcareous deposits may be present in the newly formed sclerotic tissue, and may be projected into attached tendons and fasciæ, giving rise to calcified masses closely resembling the results of the so-called **ossifying periostitis.** (See Fig. 320.) In the latter condition there are bony outgrowths (osteophytes), which are projected into the adjacent tissues and sometimes form masses of unusual size. Rarely, the outgrowth is uniform, increasing the diameter of the bone; and, as it is unassociated with a corresponding increase in length, thickening and other deforming processes may result. The compact layer always appears considerably thicker than the normal bone.

Closely allied to the suppurative inflammations of the periosteum is **periostitis albuminosa.** That the inflammation is essentially of infective origin is indicated by the frequency with which pyogenic organisms are found in the exudate; and that the infection differs from the ordinary infective processes in bone is further indicated by the course of the disease and the character of the discharge. The inflammation is not usually restricted to the periosteum, but involves the adjacent compact portion of the bone (osteitis) or the bone-marrow (osteomyelitis), and in some cases both. The discharge may show little resemblance to pus, although it frequently contains pyogenic organisms and a considerable number of finely granular oxyphile leukocytes. It is rich in albumin and contains some sugar and the usual bone salts. Ordinarily, it is fluid in character, although it may be semifluid, and on standing may coagulate as a whole or may be separated into layers, the uppermost of which appears oily, with a varying amount of coagulation in the strata below. Occasionally, the inflammatory and necrotic processes may be partly encapsulated.

Anemia, hyperemia, and **congestion** of bone are of little pathologic importance when considered as simple processes. The absence of elasticity prevents any unusual degree of vascular distention, and therefore limits the possibility of abundant arterial influx or venous accumulation. This statement does not imply that the amount of blood within the bone can not vary. Variations, however, are slight, and even with extensive inflammatory processes the evidence of vascular distention may be wanting. In general anemia, and when obliterative lesions in the blood-vessels, such as result from syphilis, have affected the arteries leading to the bone, a varying amount of anemia may occasionally be

recognized. During the active stage of osseous evolution and growth, and before the completion of development, the blood supply to the bones is relatively abundant. With the final laying-down of the osseous matrix, and later with the completion of the marrow transformation, the amount of blood present in the bone is greatly diminished. During various processes the blood supply is manifestly increased, and retardation of exit may intensify vascular distention, but the inelasticity of the Haversian canals more or less limits even inflammatory hyperemia. The changes in the bone-marrow seen in pernicious anemia have been regarded by some authorities as evidence of hyperemia. The conversion of the fatty marrow into the richly cellular marrow, as is sometimes seen in that disease, as well as in leukemia, certainly implies an increased blood supply; but here the increased supply of blood constitutes a part of the general condition, and is scarcely to be considered, in the present state of our knowledge, as a primary medullary process.

Hypertrophy of Bone.—In giants the extensive overgrowth of bone is regarded by some as essentially a process of hypertrophy. As is well known, this is at times remarkably symmetric and universal; in other instances the osseous overgrowth is restricted to one or more bones, and sometimes to the bones of a single member or to a single bone. The cause is unknown.

Acromegaly, or **pachyacria**, is a disease associated with increase in thickness and length in the long bones, with more or less alteration in many of the small bones. That the flat bones are similarly affected is shown by the increase in size of the facial sinuses. The lower jaw increases in length and thickness (prognathous jaw), and may be projected so far forward as no longer to articulate with the superior maxilla. The osseous overgrowth is usually symmetric. The spine suffers a varying degree of dorsal kyphosis. In many cases the pelvic bones and the sternum are thickened; the clavicles may be thickened and sometimes slightly elongated. The anteroposterior diameter of the chest is increased as a result of the lengthening of the ribs and posterior curvature of the spine. The slight bulging backward of the spine and projection of the sternum forward, with the drooping head and prognathism, constitute the ape-like deformity of this disease. The bones of the hand are enlarged and slightly lengthened, giving rise to the battledore hand presumed to be quite characteristic of acromegaly. In acromegaly the hypophysis cerebri usually shows some abnormality: it is sometimes the seat of a tumor, while in other cases the enlargement seems to be rather proliferative in character. The constancy with which changes are found

in the hypophysis would naturally lead to the belief that this organ is the seat of the primary lesion, but similar, if not identical, changes have been found in the pituitary body without the osseous phenomena of acromegaly.

Pulmonary hypertrophic osteoarthropathy is a condition closely allied to acromegaly, and by some is believed to be but a modified form of the latter. The club deformity of the hand is

FIG. 318.—ACROMEGALY. (Case reported by Lackey.)

Prominence of the nose with broadening of the alæ, external strabismus, prognathism, battledore hands, unusual increase in the length of the long bones (height of patient, 8 feet 6 inches), dorsal kyphosis, and marked muscular wasting are present in this case. The enormous length of the arms can be appreciated when it is stated that the patient's reach is 8 feet 9 inches; from crotch to heel the measurement is 4 feet 10 inches.

absent in acromegaly and the process is symmetric. In the disease under consideration the bones of the cranium are not involved. Marie, who first described the disease, believed it was due to the absorption of some substance from the lungs and pleura, the seat of an inflammatory process; he therefore called the disease *osteoarthropathie hypertrophiante pneumonique.*

A peculiar form of osseous overgrowth is seen in **leontiasis.** In this condition there is a symmetric enlargement of the facial

bones. The lower jaw is but slightly involved, while the bones of the trunk and extremities escape.

Aside from the conditions just described, there is occasionally observed evidence of osseous overgrowth that can not be properly considered with any of the foregoing conditions. As an example

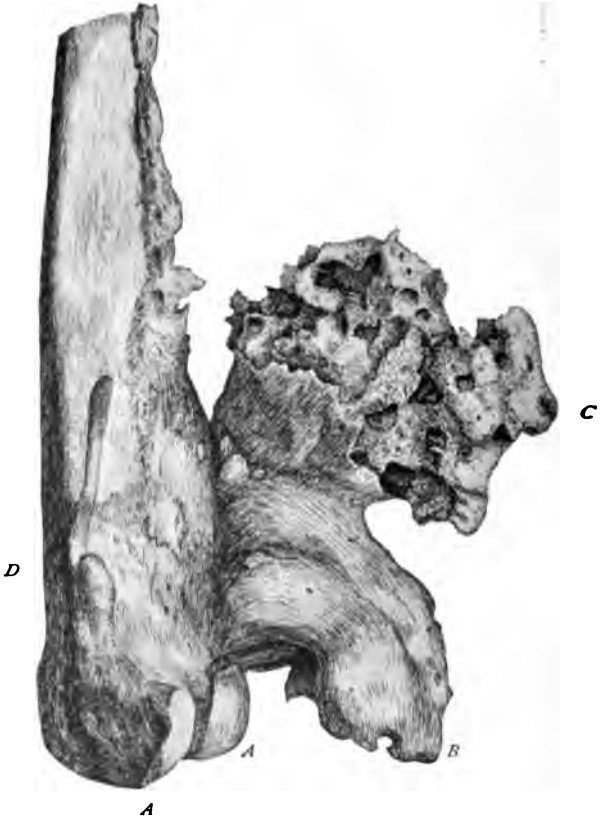


FIG. 319.—OSTEOPHYTES ON THE POPLITEAL ASPECT OF THE LOWER END OF THE FEMUR. *A*, *A*. Articular surfaces. *B*. Compact osteophyte. *C*. Spongy osteophyte undergoing caries as a result of ulceration of the overlying soft parts and extension of infection to the bone. To the right of *D* is a spicular osteophyte, and just below is a boss, evidently illustrating an earlier stage in osteophytic growth.

of this morbid condition, may be cited certain local overgrowths of bone closely resembling tumors. These may be projected from the compact portion of the bone into the marrow cavity, constituting **enostoses**; and, again, growths upon the surface of the bone projecting outward into the adjacent tissues, which,

when small, are called **osteophytes,** and when large, **exostoses.** When arising purely from the periosteum, and particularly when the origin is from the superficial layer, which has feeble bone-producing powers, these masses may be movable. Under such circumstances they are sometimes called **periostoses.** The growth of bone along the course of tendinous attachment is by some regarded as a form of hypertrophy. The osseous overgrowth resulting from inflammation, infection, and injury had probably best be considered with those processes. The overgrowth of bone resulting from the administration of such agents as arsenic and phosphorus merits no special consideration.

Atrophy of Bone.—Occasionally, atrophic processes begin in the osseous layer adjacent to the medulla, progressing externally, and constituting what is termed *eccentric atrophy.* On the other hand, the process may begin immediately under the periosteum, lessening the circumference of the bone, and in this form it is called *concentric atrophy.* In other forms of atrophy the osseous absorption occurs along the lines of the Haversian canals, and also involves, to a varying degree, the spongy layer. As a result of the widening of the Haversian canals, the bone appears spongy or porous, and the condition has received the name *osteoporosis;* the absorption following the course of the Haversian system has led to its being known as *Haversian atrophy.* As the disease is usually associated with conversion of the marrow into fatty tissue, it has been termed—probably incorrectly—fatty degeneration of bone. *Senile atrophy* attacks more particularly the vault of the skull, the scapula, and the pelvis—in other words, the flat bones. It is also seen in the inferior maxilla, and is often conspicuous in the alveolar process. As a result of eccentric and concentric atrophies the strength of the long bones may be materially lessened (*fragilitas ossium*), favoring the occurrence of fractures. Disease and injuries involving the spinal cord and nerve-trunks are sometimes followed by atrophic processes (*neuropathic atrophy*), particularly in the long bones at or near the articular extremities.

Pressure atrophy of the bone commonly results from constantly applied pressure, even of a moderate degree. Pressure of cicatrices, rapidly growing tumors, aneurysm, and fluid accumulation in cavities surrounded by bone, as in the air sinuses of the face, may be mentioned as causes of pressure atrophy. The aneurysm shown in figure 257, page 521, has caused pressure atrophy of the bodies of the vertebræ. A condition closely allied to pressure atrophy is the osseous resorption resulting from tumor formation or chronic infectious processes in the interior of the bone,

as not infrequently occurs in the inferior maxilla, where neoplastic destruction of the interior is accompanied by continuous periosteal proliferation and external apposition. A similar condition is at times observed in the long bones as a result of tumors originating in the medullary space. Under such circumstances the bone may assume enormous proportions. The femur, for example, may measure from 12 to 15 cm. in diameter and may possess externally a layer of compact bone varying in thickness, but rarely approaching 0.5 cm.

Halisteresis is probably not a true atrophic process, although it is usually considered as one of the forms of osseous atrophy, and consists, for the most part, in the removal of the lime salts with subsequent changes in the osseous matrix. It may be a more or less local affection occurring in the neighborhood of some invading processes, or it may be general, in which case it constitutes the disease called **osteomalacia, mollities ossium,** or **malacosteon.**

While osteomalacia is a disease of adults, juvenile and senile forms occur. It is most frequently observed in females, and is recognized as one of the possible complications of pregnancy. Lactation, particularly when prolonged, is believed to be a determining factor. The fact that it is endemic in certain localities has led many to believe that it is infectious in origin. In the puerperal form it is first manifest in the bones of the pelvis, to which structure it may be confined; in other cases it begins in the bodies of the vertebræ, and the first evidence may be the occurrence of lordosis, kyphosis, or scoliosis. The bone-marrow is hyperemic, and may contain areas of hemorrhage. It is usually richly cellular, and sometimes contains cysts. When advanced, the bodies of the vertebræ "may be squeezed out like a sponge," and the ribs may be bent inward. In the long bones the osseous wall may be no thicker than a sheet of paper, and can be easily indented by the finger. The pelvic deformity is commonly quite characteristic: the acetabulum is pushed inward, the iliac crest is pulled outward, the promontory of the sacrum and the pubic articulation are thrust abruptly forward. Fractures occur, and may be repaired, even during the activity of the process.

Early in the disease the histologic changes are inconspicuous. The bone salts are removed, and usually appear in excess in the urine. The first solution of the lime salts appears to occur at the periphery of the trabeculæ and around the Haversian canals. The process may therefore be considered a decalcification of the bone, but later the decalcified matrix is in part absorbed; or it may be converted into a coarsely fibrous structure.

Inflammation of Bone.—As a rule, periostitis causes a certain amount of inflammation in the adjacent osseous structures, and inflammation of the bone, approaching the periosteum, implicates that membrane. The classification and subdivisions of bone inflammation embrace: (1) Inflammation of the compact portion of the bone or of the osseous structure properly so called—a condition termed **osteitis** or **ostitis**; (2) an inflammation originating in or extending to the medullary structures, and hence called **osteomyelitis.** Periostitis, osteitis, and osteomyelitis are not infrequently associated.

The most important of these bone inflammations is **osteomyelitis.** The process is essentially an infection involving, at first, the softer and more richly cellular parts of the bone. The invading organism most frequently present is the staphylococcus, and usually the staphylococcus pyogenes aureus. In a certain percentage of cases the streptococcus is the infecting microbe. Osteomyelitis depending upon the presence of the pneumococcus, the bacillus typhosus, the bacillus coli communis, the bacillus of influenza, and occasionally other organisms, occurs. A true tuberculous osteomyelitis depends, of course, upon the tubercle bacillus. The portal of entry and the route followed by the invading organism vary in different cases. Compound fractures and wounds exposing the osseous tissues to infection by bacteria-laden agents may be taken as a type of direct infection. In preantiseptic days the disastrous results of compound fractures were due to the introduction of bacteria and the occurrence of an initial osteomyelitis that rapidly became part of a general septic process. It has been abundantly shown, however, that direct infection is not necessary to the occurrence of osteomyelitis, as the bacteria may reach the bone in other ways. Injury of the bone favors the occurrence of infection by the production of a point of least resistance, in which bacterial colonization is readily accomplished. A solution of continuity in the skin, such as is afforded by an abrasion or a superficial wound, may offer sufficient facility for bacterial ingress. In other cases no such external atrium can be demonstrated. In these instances it is assumed that the bacteria enter the circulation by means of the respiratory apparatus, or, probably in a larger percentage of cases, by the alimentary canal. The pharynx and tonsils are believed to be portals of entry. The disease is most common in the young, being especially frequent in adolescence. It occurs, however, in infancy, and less frequently in middle life or in old age. The frequency with which the young are attacked is probably owing to the

character and abundance of the vascular supply to the growing bone and on account of the very frequent occurrence of injury.

Initially, the disease attacks most frequently the long bones—the femur, tibia, humerus, and bones of the forearm, in the order given. It may be first manifested in the periosteum (periostitis), reaching the medullary cavity through the Haversian canals or the juxtaepiphyseal disc. The latter point is sometimes the beginning, and, occasionally, the disease remains limited to this area, constituting a form of osteomyelitis known as **acute infectious epiphysitis.** The vascularity of this area and its richness in venous plexuses, as well as its liability to injury, render it unusually susceptible.

With the entrance of the invading organism inflammatory processes are at once inaugurated. There is more or less vascular distention, associated with thrombosis of many of the vessels; rapid and extensive leukocytic invasion; coagulation necrosis, followed by liquefaction of the intercellular substance; and destruction of the tissue, leading to the development of purulent foci. Coalescence of these areas of suppuration, as well as extension along the tract of the marrow, lead to rapid disintegration of this substance. The extent of damage depends, as in most cases of infection, upon the virulence of the invading organism and the activity of the protective forces. In some instances the latter are insufficient, and the entire narrow cavity of the bone yields before the rapidly advancing process. The inflammation reaches and involves the periosteum, which may become detached; the nutrient vessels are thrombosed, and death (necrosis) of the entire bone follows. With inflammation of the epiphysis penetration of a joint may occur, followed by suppurative arthritis. This suppuration not uncommonly breaks through the periosteum, inducing a paraosteal abscess that burrows along the line of least resistance and eventually reaches the skin, through which it may rupture. The dead bone is called a sequestrum.

As a result of the septic thrombophlebitis, systemic dissemination of bacteria, with or without infective emboli, may give rise to the gravest form of septicemia or pyemia. The evidences of intoxication are sometimes pronounced, and death, from the overwhelming character of the poison, may precede gross evidence of the infective processes in the bone involved. Should the patient survive, with the subsidence or arrest of the more acute inflammatory phenomena, regeneration of the bone, with separation of the dead part, progresses. (See Caries and Necrosis, p. 720.)

In some instances the infective process is limited, constituting a condition spoken of as **chronic** or **latent osteomyelitis** or circumscribed osteal abscess. Such abscesses may be extremely minute, and rarely exceed from 1.5 to 2.5 cm. in diameter. They occur in the cancellous structures

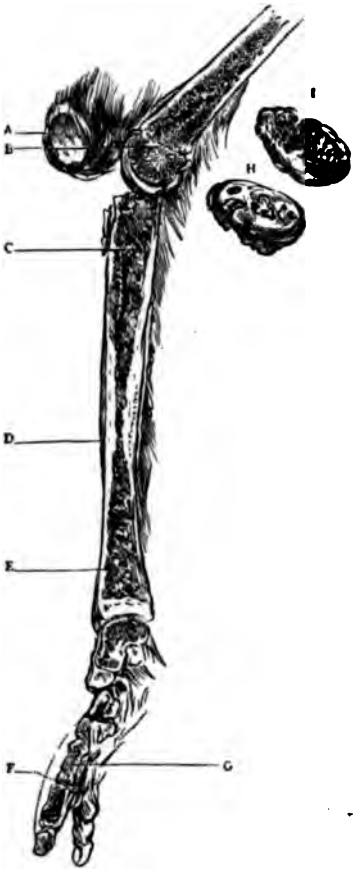


FIG. 320.—OSTEOMYELITIS INVOLVING THE TIBIA AND, TO A LIMITED EXTENT, THE LOWER END OF THE FEMUR. (The disease began at or near the epiphysis, and the case was reported under the title of acute infectious epiphysitis. The limb was amputated and the patient recovered. For detailed report see "Medical News," August 13, 1892.)

A. Patella turned backward and to one side, showing its lower surface. B. The lower extremity of the femur, showing the line of the epiphysis and a distinct border of fatty degeneration just where the epiphysis joins the shaft. In the lower extremity of the femur are several small round or irregular dots marking the position of abscesses in the bone. The periosteum of the femur is slightly thickened just above the epiphyseal line. The epiphysis is normal, except that the cartilage covering it is superficially eroded. C, D, E. Sawed section of the tibia, showing the condition of its medullary canal; at the upper extremity of the tibia the shaft terminates in a jagged, irregular extremity that has been in apposition with the epiphysis. The epiphysis is placed over on one side at H, with a view of the upper surface, while at I the under surface is shown. Just above the line leading from C are two abscesses of considerable size; below this line, and extending to the line D, is to be noted the detachment of the periosteum. The periosteum is much thickened, the thickening fading off as the line E is approached. At C the bone-marrow was intensely red (hyperemic) and there were no less than a dozen small abscess cavities; the largest of these was not 0.5 cm. in diameter. The external compact portion of the bone is much thickened, and just opposite the leader from the letter there is considerable swelling along the line of the periosteum. The lower epiphysis of the tibia does not show to advantage; at the lower extremity of the shaft, near E, can be seen several small abscess cavities. The point G is the seat of the original injury. F marks the metatarsophalangeal articulation; a section of the metatarsal bone has been made and the upper fragment has been turned downward. The great toe is also shown. H is a view of the superior surface of the epiphysis of the tibia—the articular surface. It contained not less than five or six small openings that communicated with the abscess below and with the joint above. In some of them small fragments of necrotic bone are to be observed. The cartilaginous structures of the joint are also entirely destroyed, but the articular margins of the epiphysis show a slight fragment of the two semilunar cartilages. I is the same as H, except that it is a view of the inferior surface where it came in contact with the tibia. It will be observed that the epiphysis has been converted into an abscess cavity, the wall of which is formed by a hard cancellated layer of bone and by the articular disc. There was no periosteum continuous with the shaft and epiphysis, and hence the latter moved freely upon the end of the former, thus giving rise to the "flail joint" so characteristic of epiphyseal separation. The interior of the knee contained a considerable quantity of pus, and the synovial structures were also disorganized.

of the long bones, and are more common in the upper end of the tibia than in all other situations put together. Such abscesses are usually surrounded by a zone of sclerotic or indurated bone of the densest character, and after such effort at healing-in may remain quiescent for an indefinite period. On the other hand, injury, weakened resistance, or possibly other causes may lead to recrudescence of the previously inactive focus.

After the acute stage of osteomyelitis, whether circumscribed or diffused, and also, though less frequently, after the subacute or even the chronic form, partly localized and persistent subacute or chronic infective processes may remain. These are commonly manifested by the presence of sinuses from which pus is discharged, and communicating with the external surface; or, less frequently, as in diseases of the pelvic bones, with some hollow viscus, such as the bladder or rectum. Such sinuses are walled by granulation tissue, and usually communicate with some cavity in the bone or an area of suppuration involving its exterior.

Caries and Necrosis.—The term slough is usually applied to masses of dead tissue arising in the soft parts and undergoing separation from adjacent living structures. In osseous tissue the process by which the bone is destroyed—in other words, the alterations terminating in the death of a perceptible mass of bone—is called necrosis or death of the bone *en masse*. In the soft parts the lesion accompanying and following the separation of the slough, and limited to the adjacent living tissues, is called ulceration. In bone essentially the same process is termed caries.

Causes.—Death of the bone as a result of osteomyelitis has already been considered. Periosteal separation, embolism and thrombosis, and detachment of fragments of bone from the vascular structures from which they normally receive their nutrition may cause necrosis. The principal cause of necrosis is infection. This may assume the general characteristics already described when considering osteomyelitis, or may be a chronic infectious process, such as tuberculosis and actinomycosis, or, less frequently, such bacterial invasion of the bone as may arise from the metastases of the typhoid bacillus, colon bacillus, and influenza organism. (See Causes of Osteomyelitis, p. 117.)

Toxic Necrosis.—A form of necrosis observed in laborers in match factories is usually believed to be distinct from the other types of necrosis, and is called phosphorous necrosis. It is not probable, however, that there is any material difference between this process and necroses arising from other causes. The phosphorus lessens the resisting power of the tissues, favors infection,

and as opportunities for infection are greatest in and around the teeth the inferior maxilla is most frequently involved. Caries (cavity formation in the teeth) seems to be almost a requisite, and is constantly present when the necrosis appears early.

Morbid Anatomy of Necrosis.—The masses of necrotic bone vary in size. The entire shaft of a long bone—as, for example, the humerus—may exfoliate in one piece, or only the epiphysis may be involved; not infrequently but a fragment of one or both these structures is cast off. When considering gangrene (see p. 254), attention was called to the fact that the line of demarcation was an irregular zone, one side of which bounded the living tissues and the other the dead structures, and that the changes going on within this area were those incident to the separation of the dead from the living structure, essentially a process of ulceration. This applies to the line of demarcation that would in time amputate a limb, as well as to the line of demarcation leading to the separation of a scarcely visible slough. Death of the bone and the process of separation from the living tissue are comparable to the changes already noted as present in the soft parts. Where the dead tissue joins the living there appear accumulations of phagocytic cells that attack the osseous matrix, forming the line between the dead and living structures, and proceed with the separation of the necrotic mass. Many of these cells are clearly leukocytes belonging to the phagocytes already described. (See p. 155.) Other cells resemble the giant cells, and are probably identical with the myeloplaxes of osseous absorption, and in this locality are also called *osteoclasts*. Through the secretory and phagocytic action of the leukocytes and osteoclasts the dead bone is separated from the living, and constitutes the *sequestrum*. In the mean time suppurative processes may have communicated with the exterior and formed sinuses, through which, if the piece of dead bone be small, it may escape. Commonly, the surgeon assists nature by removal of the sequestrum. Occasionally, the dead mass may be surrounded by fibrous or osseous tissue; in other words, a form of healing-in may occur.

If the infection is not arrested, destruction of tissue along the line of separation continues after exfoliation of the dead bone has taken place, and, as rapidly as granulation tissue is formed, it is liquefied by the bacteria present; and, therefore, the tendency toward repair is constantly opposed by the necrotic processes associated with the presence of bacteria. This constitutes what is called caries or ulceration of bone. The character of the pus produced by such an infection depends largely upon the microorganism present. In some cases the pus is abundant, thin, and

rich in pus-cells. This process is called *caries humida*. In other cases the amount of inflammatory exudate may be small and the discharge quite inconspicuous, to a certain extent justifying the name commonly applied—*caries sicca*, or *dry caries*.

During or after the separation of the sequestrum, and as soon as the activity of the infection will permit, the adjacent osseous tissue begins repair by the production of new bone. The new bone is commonly evolved from the periosteum, and therefore forms around the sequestrum; the latter may be covered, except that here and there are small openings through which the pus escapes; the persistence of the suppuration is due to the continuance of a low order of infection, probably kept up by the irritation of the dead bone. The newly formed bone is called the *involucrum*. The dead bone acts as an irritant, and by its removal and the disinfection of the area involved, or sometimes as a result of victory of the phagocytes over the bacteria, repair proceeds by the laying-down of new bone, which eventually replaces that destroyed by the processes of necrosis and caries. The newly formed bone is never uniform, smooth, and regular, like the normal, but uneven, clumsy, and but a crude reproduction of the destroyed tissue.

Chronic Nonsuppurative Inflammation of Bone. — In osteomyelitis, both acute and chronic, and in caries and necrosis the lesion is usually due to the presence of bacteria, the specific action of which is to induce suppuration or some necrotic and degenerative change, such as caseation. There can be no doubt that in bone a chronic productive process occurs comparable to interstitial fibroses observed in other organs. The difference, however, lies in the fact that the interstitial tissue of bone consists of a calcified matrix, while in other organs it is composed of a fibrillated structure. This particular type of inflammation is prone to occur in connection with syphilis, often when syphilitic processes are latent, and is frequently associated with the chronic productive periostitis already described. (See Fibrous Periostitis, p. 710.) It is present to a varying degree in the neighborhood of suppurative, necrotic, and infectious lesions involving the bone or paraosteal structures; it also develops around bone abscesses; in other words, chronic productive osteitis appears to result from the presence of irritants not of a kind or not sufficiently active to produce suppuration.

Morbid Anatomy.—The affected bone usually increases in size by apposition of new bone from and under the periosteum. At the same time, in the long bones—as for example, the femur—the marrow cavity is encroached upon and may be entirely re-

FIG. 321.—EXTERIOR OF FEMUR, SHOWING RESULT OF CHRONIC OSTEITIS ASSOCIATED WITH CHRONIC PRODUCTIVE PERIOSTITIS.

The growth of osteophytes over its surface is well exhibited. The bone also shows the usual deformity,—great thickening, irregularity,—and presents the marked density with which these conditions are commonly associated.

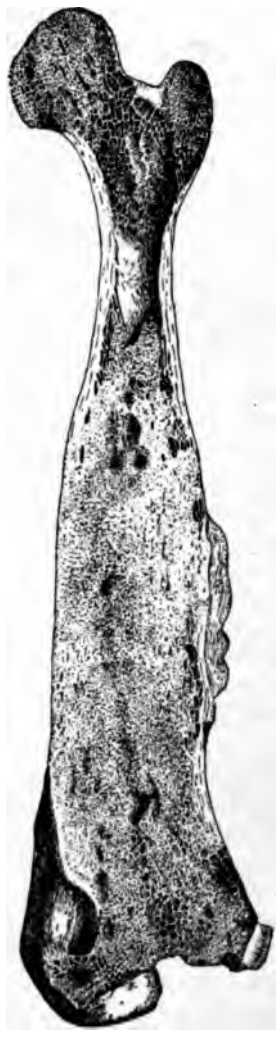


FIG. 322.—FEMUR. LONGITUDINAL SECTION OF BONE SHOWN IN FIGURE 321.

It will be observed that the lesion is restricted to about two-thirds of the bone. The marrow cavity has been obliterated by the progressive osteosclerosis. The induration of the bone was such as to require the use of a lapidary's saw for making the section.

placed by new osseous tissue. (See Fig. 322.) The new tissue is commonly hard, and the old bone becomes dense. The density may be such as to preclude incision by a chisel or saw, and as such masses occur around sequestra, they frequently give rise to great difficulty during operations for the removal of dead bone. On account of the extreme induration of the bone the disease has received the name **osteosclerosis.** By reason of its apparent inflammatory origin it has been called **condensing osteitis.** (See Figs. 321 and 322.)

Chronic Infections of Bone.—*Tuberculosis* of the bone may be manifested as an acute miliary process constituting a part of a general hematogenous (miliary) tuberculosis. In this form it is sometimes termed *acute tuberculous osteomyelitis.* The miliary tubercles disseminated through the bone-marrow histologically resemble the same process elsewhere. The most frequent form of osseous tuberculosis is chronic in character, and is the commonest of all diseases of the bone. The lesion produced, commonly known as *chronic tuberculosis of bone*, may begin in the periosteum, bone-marrow, synarthrosis, epiphyseal disc, or epiphysis. The bacilli most frequently reach the bone through the circulation. König has shown that tuberculosis of bone arises as a result of a tubercular infarct, and Müller produced such a process by the intravascular injection of tubercle bacilli. Invasion may also occur from infection of contiguous structures, and possibly through the lymphatics. The lesion is most frequently located in or near the epiphyses, through involvement of which extension to the adjacent joint may occur, constituting the usual source of tuberculous arthritis. As a result of proliferation of the fixed connective-tissue cells, as well as of leukocytic invasion, and more or less effort at peripheral vascularization, the formation of granulation tissue is brought about. Absorption of the adjacent bone occurs; Rutizky, Ribbert, and others believe that osteoclasts are not necessary to the absorption of bone in the presence of granulation tissue. Certainly, along the lines of osseous invasion in tuberculosis there is evidence clearly indicating that decalcification and removal of the bone matrix without the presence of osteoclasts are in progress. In rare instances the process becomes quiescent, with condensation of the surrounding tissue, constituting a form of healing-in closely allied to that already described on page 370. Early in the process, as a result of the specific poison produced by the tubercle bacillus, marked changes occur in the newly formed vessels, followed by caseation beginning at or near the center of the diseased area. Such caseous areas increase in size by confluence

of adjacent masses, extension into and absorption of the surrounding bone, and eventually, in many cases, perforation of the periosteum, and the induction of a paraosteal tuberculosis, thereby inducing what is often called a **cold abscess**; the manifestation in this form is usually observed in connection with tuberculosis of the hip (**coxalgia**), knee (**tumor albus**, or **white swelling**), vertebræ (**Pott's disease**), etc. Necrosis may occur. The necrotic mass most frequently, although not always, involves the whole or a part of the epiphysis. Destruction of the adjacent bone and invasion of the articular surface and joint are frequently observed, destroying the function of these structures. As a result of the destruction, erosion, or softening of the bone, distortion and deformity commonly occur. A notable example of deformity arising from this cause is seen in the spinal column, where softening of the bodies of the vertebræ gives rise to posterior arching or angular displacement (*kyphosis*). When the articular surface is reached, its destruction is almost inevitable, and, under the most favorable circumstances, there is probably nothing better to be expected than permanent ankylosis in the joint so affected.

Even in its most chronic form tuberculosis of bone presents at least two distinct dangers: (1) As in the septic osteomyelitis already described, general dissemination of the microbe may occur; in the former condition the result is septicemia or pyemia, and in the disease under consideration acute miliary tuberculosis results. In other cases the secondary manifestations may be restricted to the lungs. (2) Infection by pyogenic bacteria adds danger by augmenting the toxicity of the absorbed poison, or, rather, by adding new absorbable bodies, increasing the rapidity of the osseous destruction and rendering less efficient the protective and recuperative powers of the patient.

Syphilis of bone, as in other tissues, induces a number of lesions, many of which are so dissimilar as to render it quite impossible to establish any characteristic relation between them. Some of the lesions of syphilis are probably due to lessened resistance on the part of the economy, giving rise to the occurrence of bacterial infections that of themselves induce changes in nowise syphilitic.

In *congenital syphilis* the bones at birth, or shortly afterward, show quite characteristic changes at or near the epiphyseal line. Such changes are best exhibited in a longitudinal section of the lower end of the femur. The epiphyseal line is broadened and somewhat irregular, the irregularity being more marked on the epiphyseal side. Calcification in the neighboring areas is irregu-

lar, and proliferative changes in the adjacent perichondrium or periosteum occur, sometimes inducing a slight thickening, which, in advanced cases, may even resemble rickets. In other cases the irregular epiphyseal line assumes a grayish or bluish-white hue that, with the beginning of fatty changes, becomes faintly yellow. Spontaneous separation of the epiphysis may occur, but is infrequent. The epiphysis is usually easily detached.

Histologically, irregular proliferation of the cartilage cells can be recognized, with an associated, unevenly distributed calcification, and, later, fatty degeneration in the newly formed elements. The proliferative changes in the periosteum and perichondrium, previously referred to, with the associated enlargement, have led some observers to regard such alterations as manifestations of associated syphilis and rickets, and may have been responsible for the view that rickets is truly an evidence of syphilis—a view that has now been discarded.

Acquired syphilis induces no conspicuous bone lesion prior to the appearance of the tertiary stage. During the secondary stage there is probably some disturbance of the marrow, in common with the evident hyperplasia of other blood-making tissues, notably the lymph-glands and spleen. In acquired syphilis gummata develop most commonly in the periosteum; rarely as central lesions. Structurally, they do not differ from gummata occurring elsewhere. Degenerative and necrotic processes involving the gumma and extending to the overlying tissue may lead to external evacuation, followed by pyogenic infection. Rarely, pyogenic infection precedes the mucous or hyaline degenerative change observed in the gumma. Caseation sometimes occurs. Under appropriate treatment, and even without medication, more or less absorption may take place, which, associated with an osseous overgrowth, gives rise to osteophytic enlargement, irregularities of the surface, osteosclerosis, etc. (See Fibrous Periostitis, p. 710, and Chronic Osteitis, p. 722; also Figs. 321 and 322, p. 723.)

Actinomycosis of bone is rare in man; when present, the bones usually involved are the jaw, bodies of the vertebræ, ribs, and sternum. Occurring in the jaw, infection probably takes place through a tooth or tooth-socket. While the proliferative and necrotic changes of actinomycosis are in progress in the center of the bone, associated with resorption of the adjacent osseous tissue, subperiosteal apposition not infrequently occurs, thereby increasing the size of the bone. Suppuration, resulting from the activity of the fungus or from mixed infection with pyogenic organisms, commonly occurs. The teeth loosen and may fall

out. The tissue necrosis may extend through the oral mucosa; less frequently an external opening is formed. The discharge commonly contains the fungus, which can usually be demonstrated, except when late secondary or mixed infection produces such an excess of pus as to render the fungus difficult to find. (For Demonstration of the Fungus see page 161.) Encapsulation, as in tuberculosis, is infrequent, and the disease rarely, if ever, assumes a quiescent stage.

Leprosy of the bone is manifested occasionally as distinct leprous nodules occurring in the medulla, and may closely resemble tuberculosis. Necrosis and more or less active inflammatory processes are occasionally present, particularly in the digits.

Glanders sometimes attacks a bone. Usually, it is the periosteum that suffers, except in the septicemic form of the disease, when micro-organismal invasion of the medulla may occur.

Fractures.—The term fracture is applied to solutions in the continuity of bone or cartilage. This definition includes separation of the epiphysis, which, surgically, is grouped with fractures.

Causes.—Certain factors are recognized as predisposing; such as, for example, the position and function of bones as well as their shape and structure. Round bones are less liable to fracture than the long and flat bones, and the long bones of the extremities are more subject to injury, and hence are more frequently fractured, than the bones of the trunk. Atrophic processes and diseases associated with rarefaction increase the fragility, and hence favor the occurrence of fracture. The bones are also weakened by rickets; by cellular tumors that invade the marrow; by chronic infections, such as syphilis; by tuberculosis under certain circumstances; and by other diseases similarly influencing the density or chemistry of the bone.

The exciting cause is nearly always violence. This may be direct, as blows upon the bones, or indirect, as when the clavicle is fractured by a fall, the force having been transmitted to the injured bone through the bones of the arm and hand; in a similar way the base of the skull may be fractured as a result of a fall, the individual landing upon the feet or in a sitting posture. Fractures resulting from muscular action are typified in the fracture of the patella occurring during the act of kicking. Fractures resulting directly from disease are sometimes spoken of as pathologic.

The *line of fracture* may be transverse, oblique, or longitudinal; it may be regular or irregular. It may traverse the bone in one direction, constituting a complete fracture, or it may be a fissure, not extending through the bone in any one direction.

Bending, with fracture on one side (*greenstick fracture*), occurs in young bone. Detachment of bony prominences, such as the malleolus or trochanter, is sometimes observed. In the skull fracture associated with inward displacement of a fragment is called a depressed fracture. When the bone at one point is broken into a number of fragments, the fracture is said to be *comminuted;* when broken in a number of places, or when a number of bones are broken, the fractures are said to be *multiple*. A fracture communicating with the external air through a wound in the skin or mucosa is said to be *compound*. Certain associated conditions constitute complications, and such fractures are spoken of as *complicated fractures*. Associated injury of nerves or vessels and extension of a fracture into the joint are examples of *immediate complications;* sepsis, faulty or imperfect union, and tumor formation at the point of fracture constitute remote or *secondary complications*.

FIG. 323.—FRACTURE OF THE FEMUR, SHOWING OVERLAPPING OF THE FRAGMENTS WITH ROTATORY DISPLACEMENT OF THE LOWER FRAGMENT, AND ATTEMPTED UNION IN THIS POSITION.

As a rule, the fragments of the fractured bone do not immediately resume their normal relation one to another, and hence deformity occurs. One or both fragments may show longitudinal rotation in different directions or to different degrees in the same direction. Bending at the point of fracture (*angular deformity*) is frequently present. Lateral displacement, overlapping, and separation of the fragments are not infrequent. The rapidity and completeness of the reparative process is favored by an accurate coaptation of the fragments. That this, however, is not absolutely necessary is indicated by figure 323.

Repair of Bone.—Immediately following the injury an abundant extravasation of blood occurs; this collects around the fragments, between the ends of the compact portion of the bone, and invades, to a certain extent, the marrow. Following the

hemorrhage the initial hyperemia of repair begins. This hyperemia is most marked in the periosteum and adjacent marrow, although all the surrounding tissues show it to a moderate degree. From the hyperemic areas leukocytic infiltration takes place—the leukocytes removing the cellular detritus resulting from the destruction of tissue and the breaking down of the extruded blood. Within from forty-eight to seventy-two hours after the injury proliferative changes take place in the connective-tissue cells, particularly those of the periosteum and the bone-marrow, although similar evidences of cell activity are to be recognized in the endothelium of the capillaries. This forms the germinal or reparative tissue, certain cells of which (chondroblasts) arise from the genetic layer of the periosteum and from the medullary cavity and lay down a matrix of temporary cartilage; from the same tissues are produced other cells, the function of which, later, is the completion of osseous formation; these are called osteoblasts. The mass of new tissue is known as chondroid or osteoid tissue, and constitutes the so-called *callus*. Structurally, the callus is more or less uniform, but its position has led to a description of three different parts: The external, circumferential, encircling, or ensheathing callus is that surrounding the bone; the internal, medullary, or pin callus occupies the central canal of the two fragments; while the callus between the compact portion of the two ends is called the intermediary or ring callus. The matrix laid down by the chondroblasts is essentially a cartilaginous or chondroid tissue; it is at least a product of, if not a part of, their cytoplasm, and is shortly transformed into a marrow-like structure by the entrance of young blood-vessels. The latter are produced by budding projections from the nearest vascular twigs. (See Development of New Blood-vessels, p. 299.) The final step in bone production consists in the calcification of the osteoid matrix. New marrow is formed by the projection of

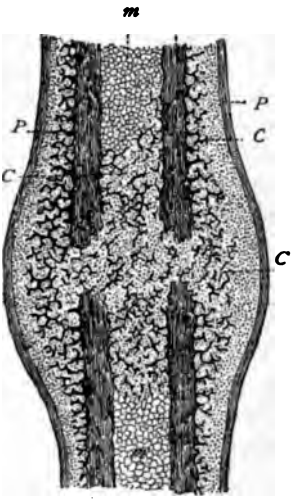


FIG. 324.—TEN-DAY-OLD FRACTURE.—(*Schmaus.*)

m, *m*. Bone-marrow. *P*, *P*. Partly detached periosteum. *C*, *C*, *C*. Deposit of osteoid and chondroid tissue under the periosteum and extending between the ends of the two fragments and into the medulla—the callus.

blood-vessels bringing with them a mantle of marrow-cells. From these, and possibly from the proliferation of adjacent cells with the abundant growth of new blood-vessels, the marrow cavity is reestablished.

Absorption of irregular and useless spicula begins early in the process, and is carried on by the leukocytes and osteoclasts already mentioned. After a time, varying in different cases, removal of the ensheathing or temporary callus takes place. This is accomplished through the intervention of the osteoclasts and chondroclasts, and requires, not uncommonly, many months for its completion. Wide separation of fragments, defective immobilization, the presence of muscle or other soft tissue between the fragments, and inherent deficient reparative power on the part of the tissues may prevent complete union. The degree of faulty union varies. Sometimes after weeks there has been no perceptible effort at repair; in other cases fibrous tissue firmly joins the two ends, constituting *fibrous union*, which later, with rounding-off of the ends of the bone, may give place to a false joint (*pseudarthrosis*). Excessive callus-formation may lead to the coalescence of the reparative tissues arising from fractures of parallel bones at the same level, and, later, may firmly unite all the fragments, constituting a synostosis.

Rickets; Rachitis; Rachitismus; Morbus Anglicus.—Rickets is a disorder of nutrition in which the process of growth in the bones, muscles, mucous membranes, and many other tissues is profoundly influenced. The disease is not primarily one of bone. The changes seen in the bones are dependent upon defective nutrition during the period of most active osseous growth.

Etiology.—Rickets is a disease of childhood, usually manifesting itself toward the end of the first year, and nearly always before the end of the second or third year, although rare instances are reported in which the disease showed its first manifestations as late as the ninth year. Neither syphilis, unsanitary surroundings, disorders of the digestion, nor heredity are sufficient causes, although, with the exception of the last named, they may intensify the activity of the process. As the disease is not restricted to the human family, but also occurs in monkeys and in lions' whelps, certain experimental observations have been made. The experiments of Cheadle and Bland Sutton seem to indicate that, at least in lions, the morbid condition may be avoided by the use of a diet rich in cream, proteids, and earthy phosphates. The necessity for fat in the diet seems to be thoroughly established, and the fact that children become rickety on a diet containing fat

is presumed to depend upon the presence of associated digestive disturbances that prevent the emulsification and consequent absorption of this body; therefore changes in the diet after the occurrence of catarrhal processes in the alimentary canal often fail to modify the disease.

Morbid Anatomy.—A conspicuous and usual change is the development of the *rachitic rosary*, which consists of an enlargement appearing at the point where the rib joins the costal cartilage, usually more marked on the inside than on the external surface, and commonly conspicuous at the junction of the fifth and sixth ribs with their costal cartilages. This enlargement has been recognized in the fetal skeleton, and is sometimes present at birth. The *craniotabes* of Elsasser consists of absorption and thinning of the cranial bones, most marked in the parietal and occipital regions. The marginal membranous portions of the bone do not show the normal progressive ossification. Associated with the absorption of the inner table and the thinning, there also occur hyperplastic changes, swellings, or bosses over the frontal, parietal, or occipital bones. The sutures, excepting the mediofrontal, show delayed union, and the anterior fontanel may remain open until the end of the second year or even later. The teeth appear late and frequently not in their proper order. They become carious early. In addition to the rachitic rosary, already mentioned, the chest shows flattening on the sides, and the sternum is thrust forward (*pigeon-breast*). Posterior and lateral curvature of the spine occur. The iliac crest may be thickened and the pubic arch may be narrowed. Juxtaepiphyseal enlargements similar to those observed on the ribs appear in the long bones, particularly the radius, ulna, tibia, and femur. The periosteum seems more vascular than normal, and strips off with unusual readiness. The underlying bone is commonly soft, and frequently bends; greenstick fractures may occur.

Histologically, there is evidence of "excessive preparation for bone formation which does not occur" (Jenner). Osteoporosis, depending upon lacunar absorption, is present. Unusual periosteal production of osteoid tissue gives rise to osteophytes that, with the appearance of recovery, are converted into bone, thus perpetuating the deformity produced by their growth. The line of calcification in the juxtaepiphyseal cartilage is irregular, poorly marked, or may be absent. There is an abundant production of osteoid matrix, into which medullary vessels are projected without the usual accompanying deposit of bone.

In addition to the osseous changes already mentioned, the ligaments of the joints are lax and frequently give way. Th

muscles usually show deficient and imperfect striation, and during life are weak. The liver and spleen are not infrequently enlarged, and commonly show increase in fibrous tissue. More or less evidence of associated catarrhal inflammation of the mucosæ is usually present.

THE JOINTS.

A **joint** is composed of the articular ends of two or more bones; of the capsule, ligaments, or other structures binding the bones together and retaining them in their proper relations one to the other; and of the synovial membrane, the function of which is to lubricate the surfaces. The ends of the bones entering into the articulation are commonly covered by articular cartilages, and may be further protected by intermediary structures not properly belonging to either bone. The capsule and ligaments are composed of fibrous tissue more or less rich in elastic elements, dense and firm, offering certain protection to the joint and resisting intra-articular accumulations. The synovial or serous membrane of the joint possesses an outer layer of elastic fibers and fibrillar tissue, continuous with that of the adjacent structures, and an exposed layer of flattened endothelial cells.

Malpositions and malformations of the joints may be congenital or acquired. The congenital malformations are usually dependent upon developmental arrest, involving particularly the articular surfaces, and are manifested by such deformities as club-foot, knock-knee, club-hand, etc. The acquired malpositions and malformations are either the result of disease that more or less profoundly alters the bone, or of trauma, relaxation of the ligaments, or unusual or abnormal muscular contraction or other applied force leading to altered relations between the articular surfaces and constituting a lesion called a **luxation.**

Fatty, hyaline, and **mycoid degenerations** occur in the synovial membrane, and occasionally in the articular cartilage. The hyaline material may resemble lardacein, even to the extent of yielding the appropriate reactions. Fat accumulates in the synovial fringes, and later the same may be converted into cartilage or chondroid substance.

Metaplasia of the cartilage into fibrous, mucoid, or osteoid tissue occasionally occurs, and in rare instances it may be, in part at least, converted into a marrow-like substance.

Infiltrations into Joint Structures.—*Calcareous infiltration* not infrequently follows reparative processes in the neighborhood of a joint and inflammations of the joint capsule and synovial membrane, particularly when chronic, and also occurs as a result

of chronic infection, notably tuberculosis, either of the joint or of an adjacent structure. The condition is sometimes noted in old age independent of evident gross lesions of inflammation.

Hemorrhage into the joint (**hemarthron**) or into any structure of the joint is frequently associated with the presence of pigment held in the matrix of the cartilage and fibrous tissue as well as in the capsule of the normal cartilage cell. Reference has been made to the uratic deposits occurring in the cartilages in gout. (See p. 238.)

Loose Bodies in the Joints.—These are occasionally seen in the joints of the elbow, wrist, hip, shoulder, and ankle, but in from eighty-five to ninety per cent. of the cases the knee-joint is affected. Their presence in arthritis deformans has been referred to. They may result from detachment of the articular cartilage, or may consist of a fragment of bone or synovial fringe that has become cartilaginous, fibrous, or lipomatous, or they may be produced by the exfoliation of fibrinous, calcareous, or inflammatory masses. Loose bodies are usually small and irregular, rarely attaining the size of two or three centimeters. They are sometimes multiple. The structure is largely dependent on the origin, as indicated by the foregoing list of causes. Occasionally, a loose body may be attached.

Inflammations of Joints.—Theoretically, inflammatory processes may be restricted to any one of the tissues entering into the formation of the joint, or they may involve some or all of the structures. Inflammation of the cartilage is called *articular chondritis;* inflammation of the synovial membrane, *synovitis;* inflammation of the joint capsule and ligaments, *parasynovitis;* while inflammatory processes involving all these structures are grouped under the name of *panarthritis.* Chronic inflammatory processes or inflammations of a low grade may be restricted to one of the foregoing structures, but joint inflammations are rarely simple processes, and usually mean more or less involvement of all the structures.

Inflammations of the joints may be restricted to a single joint (*monarticular arthritis, monarthritis*), or a number of joints may be simultaneously affected, or in quick succession (*polyarticular arthritis*, or *polyarthritis*).

Acute simple serous synovitis is an inflammatory process not due to pus-producing organisms, or at least to pyogenic bacteria of such virulence as to lead to the accumulation of finely granular oxyphile cells (pus); whatever the cause may be, it gives rise to a more or less abundant serous or synovial accumulation in the joint cavity or adjacent bursæ, or both.

Etiology.—Such injuries as contusion, sprain, pinching of the synovial folds, loosening of articular cartilages, and loose bodies in the joints may be taken as types of the purely local causes. A similar, although possibly not identical, inflammatory process is induced by the presence in the circulation of irritants, either bacterial or chemic or possibly both. The joint inflammation of acute rheumatism partakes of many of the characteristics of an acute serous synovitis. The inflammatory process in gonorrhea is usually associated with the abundant migration of finely granular oxyphile leukocytes, and hence justly should be considered with the suppurative form of arthritis, although cases occur essentially serous in nature.

Morbid Anatomy.—The process may be monarticular or polyarticular. It is most frequent in the large joints having complicated internal structures, and particularly those subjected to the greatest strain and most liable to injury. Such joints are those of the knee, ankle, elbow, and wrist. The initial manifestations are usually in the synovial membrane. There is probably at first a scantiness in the synovial secretion, associated with hyperemia of the membrane, the bright red surface of which contrasts strongly with the pearly-white articular cartilages. The first fluid extruded is usually quite clear, but later is cloudy from the addition of migrated leukocytes and desquamated endothelial cells. Erythrocytes are occasionally present, particularly in the earlier stages. The synovial inflammation partakes of all the characters and variations occurring in inflammation of serous membranes, and hence may be serous, dry, fibrinous, or serofibrinous. (See Inflammation of the Pericardium, p. 474.) The amount of fibrin varies; occasionally, the disease runs its course without the presence of fibrin in the fluid drawn off. On the other hand, extensive fibrinous deposits may occur, and these, going on to organization, may form adhesions, may thicken the synovial membrane, and, with added connective-tissue elements in the capsule and lessened secretion, may induce a form of fibrous ankylosis. Ankylosis is more likely to occur in the dry or fibrinous type of this disease. Occasionally, a serous accumulation persists for a long time in the joint, constituting a form of effusion called **hydrops arthrosis.** In the dry form, and occasionally in the serous form, when associated with fibrinous deposits, loose masses of fibrin are found; sometimes these are attached to the long, thread-like fimbriæ of the synovial membrane. Under more favorable conditions the serum may be absorbed, the fibrin, if small in amount, may degenerate or be absorbed, and the joint may return to the normal state; subsequently, such

joints usually possess a rather high degree of susceptibility to irritation.

Acute Suppurative or Purulent Arthritis.—As elsewhere, suppuration of the joint may be produced by the injection of purely chemic bodies. That such a process is ever induced, except experimentally, does not seem probable. Infection by any of the pyogenic bacteria may bring about this condition; as causes the pyogenic cocci should be first mentioned; the gonococcus, pneumococcus, bacillus coli communis, typhoid bacillus, and occasionally other organisms, may induce a suppurative arthritis. The infection may reach the joint through a wound communicating with the surface. In other cases a peri-articular suppurative process involves the joint. Occasionally, suppurative foci in or near the articular end of the bone penetrate the joint. (See Fig. 320, p. 719.) In other cases the joint is infected through the blood; as examples of hematogenous infection may be cited suppurative forms of gonorrheal rheumatism, and the joint complications of pneumonia, septicemia, and pyemia.

Morbid Anatomy.—Like the simple acute form, the disease may be monarticular or polyarticular. While it is not improbable that the disease begins as a synovitis, in a large number of cases it quickly becomes a panarthritis. The initial stage of the process closely resembles that observed in the acute serous synovitis. The hyperemia is usually more marked and the leukocytic migration far in excess of that usually seen in the synovial inflammation described. In the latter condition the large hyaline cell is usually most abundant, while in the suppurative form the finely granular oxyphile is the predominating leukocyte. The distention of the joint may be marked. Erosions in the cartilage occur, sometimes associated with exfoliation (necrosis) of some size. Occasionally, the whole epiphysis may be detached, particularly when the original focus was in the bone. Necrotic spots appear in the joint capsule; these, when extensive, may lead to its disintegration, withdrawing the normal support of the joint and permitting luxation (*pathologic luxation*); later, peri-articular suppuration is induced, which may involve the adjacent tendons, tendon sheaths, and bursæ, burrowing along the course of such structures or presenting at the surface as a peri-articular abscess. The extent of damage to the joint is largely dependent upon the activity of the process, but more particularly upon the length of time it is allowed to progress without evacuation of the inflammatory accumulation. The early withdrawal of the infection favors the progress of repair; if, however, it be permitted to persist, erosion of the articular ends of the bone occurs, with the

destruction of the synovial membrane and joint capsule, leaving little better to be hoped for than a more or less firm fibrous ankylosis in which extensive calcareous infiltration takes place, resulting in what is practically a bony ankylosis.

Gouty Arthritis.—The articular inflammation occurring in gout is in part a serous synovitis associated with the precipitation of sodium biurate upon and in the articular cartilages, and also, although not to the same extent, in the joint capsule and ligaments and synovial membrane, and occasionally in the peri-articular structures as well. Late in the process the peri-articular deposit is constant. The acicular crystals are deposited in the cartilaginous matrix and in the capsules of the cartilage cells, as well as upon the free surface. The cartilage near and upon the adjacent bone escapes. The deposit may occur in normal cartilage, and the late degenerative processes, terminating in erosion, exfoliation, or necrosis, are truly secondary to the irritation of the urate present. From the experiments of Garrod and from other studies it would appear that the uratic deposit came from the synovia rather than from the osseous or cartilaginous tissues themselves.

That the synovial membrane is not the tissue essentially at fault is shown by the fact that deposits also occur in the eyelid, ear, and nose. The clinical notes would lead to the belief that the deposits occur only before and during paroxysm. Associated with deposit of biurate, or probably secondary to the necrosis that it causes, deposition of calcium carbonate and phosphate also takes place. These sometimes induce peri-articular enlargement, constituting the so-called *tophi*. The gouty inflammation is most frequent in the metatarsophalangeal joint of the great toe. When the deposit reaches the surface, infection followed by suppuration occasionally ensues. The discharge commonly contains the needle-like crystals of sodium biurate. (See Uric Acid Deposits, p. 238.)

Osteoarthritis; *chronic arthritis; arthritis deformans; rheumatoid arthritis; dry arthritis; trophic arthritis; spondylitis deformans* (vertebræ), are all synonyms indicating the Protean manifestations of the disease, or expressions of the various views that have been held as to its cause. Osteoarthritis may be monarticular or polyarticular, and may, in certain stages of its evolution, resemble acute rheumatism and gout. In the monarticular form the hip, knee, shoulder, and elbow most frequently suffer. The polyarticular form is a disease of the smaller joints of the extremities and of the vertebræ. The inception of the disease frequently occurs early in adult life, and is usually preceded

by a history of trauma, sometimes rheumatism; but the essential etiologic factor is still unknown. Bacteria have been described as present, and by some are believed to cause the condition. The disease is a panarthritis, usually beginning in the articular cartilages by proliferation of the cartilage cells and, later, leading to the formation of a fibrillated matrix; the fibrillation is particularly marked on the surface of the cartilage, which is thereby given a velvety aspect. Absorption, exfoliation, and necrosis of the proliferated cartilage appear later. From the margin of the cartilage the process extends to the synovial membrane, the connective tissue of which may proliferate and lay down a chondroid or osteoid matrix, in which calcific deposits form. The villi of the synovial membrane become exuberant, and not uncommonly loaded with fat, constituting the so-called arborescent lipoma. As a result of myelogenous absorption and lacunar atrophy, the density of the articular end of the bone is lessened, and, later, gelatinoid or mucoid areas develop in its interior. Excavations occur on the articular surface that, with lateral extensions from the periphery of the articular cartilages, entirely destroy the architecture of the joint. Osteophytic growth from the bottom of the acetabulum, with lateral extensions from the head of the femur, entirely change the character of the joint, the acetabulum becoming the ball and the femur forming the socket. Such alteration in the joint is not at all characteristic or constant, but is mentioned as illustrating the remarkable deformity with which the process may be associated. Detachment of portions of osteophytic growth and loose cartilages with the detachment of fimbriæ give rise to loose bodies in the joint. The extensive production of osteophytes may lead to fixation or even to ankylosis, while the osseous resorption may favor the occurrence of luxation or may weaken the bone in the neighborhood of the joint, permitting fracture. Atrophy of muscles and wasting of adjacent structures make more evident the articular deformity.

Neuropathic Diseases of Joints.—*Spinal* and *neurogenous arthropathies* are forms of joint-change commonly associated with locomotor ataxia, with syringomyelia, and less frequently with compression, concussion, and other lesions of the spinal cord, including degenerative change in the anterior horns. The disease is monarticular in about eighty per cent. of the cases, and usually involves the larger joints,—namely, the knee, hip, shoulder, or elbow,—although it is occasionally seen in the smaller joints of the hand and foot. In some cases osteophytic growths occur, usually beginning in the cartilage and cellular elements of the capsule and peri-articular tissues. This constitutes the

so-called hypertrophic form. In the atrophic form degeneration and absorption of the articular surface and part of the adjacent bone occur, with relaxation of the ligaments, permitting or favoring luxation. The head of the bone—as, for example, the femur—may be completely absorbed. Serous effusion into the joint may be present; it is commonly not marked, except in the earlier stages. The disease was studied by Charcot, and is frequently spoken of as *Charcot's disease of the joints.*

Chronic Infections of Joints.—Tuberculosis of joints is also called articular tuberculosis, tumor albus, white swelling, scrofulous or strumous joint disease, fungous disease of the joint, caseous arthritis, tubercular abscess of the joint, cold abscess of the joint, etc. The condition is most frequent in children—over eighty per cent. of the cases occurring before the fifteenth year. The disease commonly attacks the hip, knee, or ankle, although the shoulder, wrist, and elbow occasionally suffer; a process practically identical, affecting the vertebræ, is called *Pott's disease of the spine.* The disease is nearly always monarticular; to this, however, there are occasional exceptions. A history of trauma may be present; the injury may induce an inflammation that later becomes infected by the tubercle bacillus; it is also probable that a latent or quiescent area of tuberculosis in the adjacent bone may assume renewed activity as a result of trauma. It is usually held that the tubercle bacilli reach the area involved through the circulation, coming from a primary lesion elsewhere, as, *e. g.*, a latent tuberculosis of the bronchial glands, or possibly mesenteric lymph-nodes. As already indicated (p. 724), the initial lesion of the process is usually in the adjacent epiphysis, from which it extends to the involved joint, constituting the so-called *osteopathic* variety of the disease. In other cases the disease appears to arise in the synovial membrane; in other words, it is a primary involvement of the joint, and is called *arthropathic.*

Morbid Anatomy.—Whether involving the joint from adjacent bones or beginning as a chronic synovitis, the process rapidly becomes a panarthritis. The disease is occasionally preceded by a stage of hydrops arthrosis. The abundant production of granulation tissue occurs not only from the synovial membrane, but the fungoid mass may be projected from the tuberculous bone, thus filling the joint with granulation tissue containing, in its earlier progress, numerous tubercles in various stages of evolution. In this tuberculous tissue caseation rapidly ensues, distending the joint by accumulated caseous detritis. The joint capsule is more or less rapidly invaded; and further extension of the process,

along the line of least resistance, frequently occurs. Like other forms of tuberculosis, the lesion may be arrested, and healing-in may occur at any stage of its evolution. In the majority of cases, however, destruction of the joint takes place. The articular extremity is usually riddled by perforations from which the granulation tissue projects, or such openings communicate with the caseous areas in the adjacent zone. Epiphyseal separation is sometimes observed. With healing-in extensive calcareous infiltration takes place, terminating in permanent ankylosis.

The dangers of tuberculous arthritis are twofold. In the first place, the local tuberculous lesion may give rise to general miliary tuberculosis as a result of the hematogenous dissemination of the tubercle bacillus. Extensions along the bone may lead to tubercular osteomyelitis, caries, and necrosis; and disastrous complications follow infection by pyogenic organisms. The weak protective powers present in the diseased tissues favor the rapid dissemination of bacteria, and there may be added to the local tuberculosis one or more of the dangers incident to acute infectious osteomyelitis.

Ankylosis is the name given to that condition in which a joint becomes useless by reason of fixation. The name literally indicates angular deformity, which may or may not be present. When the fixation is dependent upon lesions around the joint, upon fibrous changes in the joint capsule, or upon muscular contraction and similar conditions, it is said to be a *false* or *pseudo-ankylosis*. On the other hand, when the fixation arises as a result of structural changes in the articular surfaces, leading to osseous or calcific union between the bones entering into the joint, the condition is called *true ankylosis*. Such ankylosis commonly follows protracted inflammatory processes affecting the joint, suppurative arthritis, tuberculosis, and similar inflammatory or necrotic processes.

Morbid Anatomy.—The alterations observed in the joint depend largely upon the cause. Theoretically, in false ankylosis the articular surfaces are normal. There is usually considerable increase in the fibrous tissue of the capsule, which may be also calcareous. Further, the capsule adapts itself to its long-continued quiescent position, and, with the removal of the cause, if such be possible, considerable time is necessary for the reestablishment of pliability and elasticity in the altered ligaments. In true or osseous ankylosis there may be formation of new bone or extensive calcific deposits in granulation tissue, giving rise to fixation. Fractures involving joints may, in the presence of union, permanently fix the articular surfaces. Extensive calcareous infiltration of inflammation with more or less attempt at osseous repair may entirely destroy the articular structures.

CHAPTER XVI.

THE NERVOUS SYSTEM.*

General Considerations.—*Anatomy and Histology.*—It is not within the province of this book to discuss in a detailed or minute manner the anatomy of the nervous system, and those who desire such knowledge are referred to anatomies and special text-books on the subject.

The nervous system is composed of (1) the *brain* and *spinal cord*, which together constitute the *central nervous system*, and (2) the *peripheral nervous system*, consisting of multitudes of nerve-fibers that are projected in small bundles, known as *nerves*, from both the brain and cord to the various parts of the body; in addition to the foregoing, there is what is known as (3) the *sympathetic nervous system*, which, although probably developed independently, is to be regarded as an appendage of the peripheral nervous system.

The brain and cord are covered by three fibrous investments, collectively known as the *meninges;* these are in intimate relation with the structures that they inclose, and are to a certain extent influenced by many of the diseases of the brain and cord, which structures are also affected in a number of lesions beginning in the overlying membranes.

The covering directly in contact with the surfaces of the brain and cord is called the *pia mater;* next to which is a layer of extremely delicate tissue directly continuous with the foregoing, and, therefore, to be regarded as really a part of it, known as the *arachnoid;* and, finally, covering the inner surface of the skull and lining the bony wall of the spinal canal is a very dense, comparatively thick membrane, which has received the name *dura mater.* The membranes around the cord are continuous with those covering the brain, of which they are merely prolongations; these membranes, though becoming much thinner, and in part losing their identity, are further prolonged as coverings of the nerves passing from the brain and cord; the dura becomes the *epineurium;* the arachnoid, the *perineurium;* and the pia, the *endo-*

* For method of examination see pp. 38 to 44.

neurium. Although it should be clearly understood that the several membranes constituting the meninges are respectively the same in both the brain and cord, it is equally important to know that they differ from one another in several minor particulars.

Histology of the Membranes.—The pia and arachnoid are made up of delicate bundles of fibrous tissue, upon which lie many small, flattened cells; the outer surface of the arachnoid is covered by a continuous layer of flattened endothelial cells. Processes from the pia penetrate the nervous substance of both the brain and cord; these processes carry blood-vessels, and become continuous with the peculiar supporting structure of the central nervous system, known as the *neuroglia*. From the surface of the arachnoid, especially on each side of the superior longitudinal fissure, bulbous projections occur; these penetrate the dura, and are called the *Pacchionian bodies*. Both the pia and arachnoid are extremely vascular; the blood-vessels are particularly numerous in those prolongations of the former that enter the ventricles, and are called the velum interpositum and the choroid plexus. The velum interpositum and the choroid plexus are covered by cuboid epithelial cells, which in the new-born are ciliated.

Both the inner and outer layers of the *dura* are made up of compact bundles of fibrous and elastic tissue—those in the outer being placed transversely to those on the inner coat. This coat contains only a few blood-vessels.

The **brain** comprises those parts of the central nervous system within the cranial cavity; they are the *cerebrum*, the *cerebellum*, the *pons varolii*, and the *medulla oblongata*—the last of which passes into the spinal canal, and becomes continuous with the spinal cord. The brain as a whole is oval in form; the upper surface, although very uneven, presents a fairly regular convexity, while the under surface is somewhat flattened and is much more irregular in appearance. The average weight of the adult brain in man is 1359 gm., and in woman, 1235 gm. While it is true that considerable variation from the foregoing in either direction is not inconsistent with perfect health and even with great intellectual activity, the brains of idiots and of the intellectually feeble are, as a rule, considerably below the average weight.

The **spinal cord** extends from the medulla to the point where it breaks up into a number of nerve bundles known as the cauda equina; this takes place opposite the body of the second lumbar vertebra. The cord is about eighteen inches long and weighs

about thirty grams. As a whole, it is irregularly cylindric in form, tapering at its lower end, and forming what is called the *conus medullaris*. Anteroposteriorly it is somewhat compressed; in the cervical and lumbar regions it swells slightly, producing dilatations known as cervical and lumbar enlargements respectively. It is divided in front by a groove, called the anterior median fissure; and behind by a septum, termed the posterior median septum (posterior median fissure of some authors). Two quite distinct furrows are situated on the posterior aspect of the cord at the points of exit of the posterior nerve-roots, which is a little external to the median septum; these depressions are called the *posterolateral grooves*. Anterior fissures corresponding to the point of origin of the anterior nerve-roots are described by some authors; recent researches into the location of the different functional tracts of the cord go to show that the anterior and lateral columns are physiologically identical; and, further, as there is no sufficient anatomic reason for the belief in a distinct fissure along the line of exit of the anterior roots, its description seems unnecessary.

The **nerves** arising from the brain and spinal cord consist of a number of separate bundles of nerve-fibers, each of which is incased in a sheathing of fibrous tissue, and all the bundles are connected and surrounded by an outer layer of fibrous tissue which becomes continuous with the neighboring structures.

Histology of the Nervous System.—The entire nervous system, in both man and lower animals, consists of multiples of a single element (the **neuron**), made up of a cell—the *nerve cell* or *ganglion cell*—and numerous *processes*, one of which, in certain varieties of the cell, becomes the *axis-cylinder* of a nerve, and in this form extends to the point of peripheral distribution; notwithstanding that these cells are all fundamentally identical, certain later differentiations occur, giving rise to morphologic and tinctorial differences, justifying their division into a number of varieties. The nerve elements proper are united by a tissue called the **neuroglia.** The neuroglia consists of numerous small cells between which are multitudes of fibrils that probably have no connection with the cells; the relation between the fibrils and cells is, however, so intimate that the former have been generally described as processes of the latter, and together they are spoken of as *moss* or *spider cells*, depending upon their individual peculiarities.

The neurons and neuroglia cells are believed to be derived from the epiblastic tissues of the body, and should be looked upon as but modified epithelial cells.

Ganglion cells are found principally in the gray matter of the central nervous system, but are also present in the sympathetic ganglia, in the ganglia occurring in the course of cerebrospinal nerves, and in the organs of special sense. The cells vary in size from 4 μ to 135 μ. There are a few oval or spindle-shaped ganglion cells, but the vast majority has an irregular form, due to the abundant processes that emanate from them. Cells having a single process are called unipolar (occur in man in the olfactory mucous membrane); if two processes are present, they are termed bipolar; and if more than two, multipolar. The processes projecting from one end of a ganglion cell, after proceeding a short distance, break up into numerous smaller branches, known as dendrites, which again subdivide, and their smallest processes exhibit multitudes of minute projections termed gemmulæ; the former have not inaptly been compared to the limbs of a tree, and the latter to the leaves. From the other end of the nerve cell another process passes out, which may continue as an *axis-cylinder* of a nerve-fiber, or, after going a short distance, may turn on itself and break up into a number of processes resembling the dendrites of the opposite end. Cells the processes of which become axis-cylinders are called *cells of the first type*, and those whose processes fail to form axis-cylinders are termed *cells of the second type*. All the peculiarities of the ganglion cells so far mentioned can be brought out with distinctness only by the method of preparation devised by Golgi. This method, as slightly modified by Berkley, is as follows:

To get good results the tissue must be perfectly fresh. It should be hardened in Müller's solution (see p. 49) until it becomes sufficiently hard to admit of fairly thin sections being cut; this requires, at ordinary temperatures, about two weeks. The fluid should be abundant and should be changed daily for the first few days. The tissue is then cut into pieces of not more than three millimeters in thickness, and is placed in the following solution, which should be freshly prepared:

Bichromate of potassium, 3 per cent. solution in water, 100 parts.
Osmic acid (OsO_4), 1 per cent. solution in water, . . 30 "

After three days remove the specimens and imbibe the excess of the foregoing solution with filter-paper; wash for a few minutes in a weak solution of silver nitrate in water. The tissue is now placed in the following solution:

Phosphomolybdic acid, 10 per cent. solution in water, 2 drops.
Silver nitrate, 1 per cent. solution in water, ... 60 c.c.

This mixture should be prepared just before being used. In the mixture the tissue should remain undisturbed for two or three days, or, if desirable, it may be kept indefinitely by adding a few drops of the silver nitrate solution at the expiration of the time mentioned. During the process of preparation it is perhaps better to keep the jars containing the mixture in the dark. Impregnation goes on best at about 25°C. After the foregoing the tissues are placed in absolute alcohol for an hour and are then embedded quickly in celloidin. (See p. 59.) Sections are examined without staining. By this method the nerve cell and its processes are stained a uniform brownish-black color. The stain is at best very capricious—some of the cells staining intensely and others in the immediate vicinity not at all. The neuroglia cells and the fibrils around them are also stained. Golgi's method is useful only as a stain for the outlines of the cells and their processes, and it therefore becomes necessary to employ other means if it is desired to study the internal structure of the cells.

The ganglion cells have no distinct cell-membrane. They contain a reticular protoplasm that stains with acid dyes; in the greater number of them is found, within the reticulum, a substance that takes basic dyes intensely. These basophilic masses are called the **bodies of Nissl.** In the great majority of nerve cells the nuclei do not take basic stains; they contain a delicate reticulum and a nuclear wall, both of which are acidophilic. As a result of this, the nucleus has almost the appearance of a round, open space where the tissues are stained in the usual way. Within the nucleus is a nucleolus that stains intensely with basic dyes.

Nissl classifies nerve cells into (*a*) **karyochromes,** or cells the nuclei of which take basic stains; and (*b*) **somatochromes,** or cells only the protoplasm of which takes the basic dye. The former are comparatively rare, but are found in the olfactory lobe, the cerebellum, and the retina. The latter have been subdivided into several different varieties, depending upon the arrangement of Nissl's basophilic or, as they are also called, chromophilic bodies: (1) *Arkyochromes,* or cells in which the chromophilic substance is arranged in rows; (2) *stichochromes,* or cells in which the chromophilic substance is arranged more or less regularly throughout the cell; (3) *gryochromes,* or cells in which the chromophilic substance occurs in fine granules; (4) *arkystichochromes,* or cells in which some combination of the preceding is present.

The chromophilic substance is, as a rule, tolerably uniformly distributed throughout the cell; it is, however, worthy of note

that just beneath the point where the axis-cylinder process emerges from the cell this substance is largely absent. In conclusion, it should be noted that in many ganglion cells there are small collections of yellowish-brown pigment, situated in the protoplasm just outside of the nuclear wall; the quantity of this pigment increases with age and under pathologic conditions.

Method of Demonstration.—The method first employed for the purpose of demonstrating the previously mentioned peculiarities of ganglion cells was that of Nissl. Blocks of tissue not over one centimeter in thickness are hardened in 96 per cent. alcohol. The hardened tissue is removed from the alcohol and gently blotted with bibulous paper; dip the piece of tissue in thick celloidin (p. 60) and attach it to a block prepared as directed. (See p. 60.) Do not embed. Harden the celloidin in 96 per cent. alcohol and section with knife wet in alcohol of the same strength. (For directions as to cutting celloidin sections see p. 60.) Preserve sections in 90 per cent. alcohol. The stain used is a soapy solution of methylene-blue (methylene-blue, B. patent), and had best be purchased as prepared by Grübler, who has placed it on the market under the name "Soapy Solution of Methylene-blue, Nissl." The sections are placed in this solution and heated until bubbles form; they are then washed in a mixture composed of anilin oil (10 parts) and 96 per cent. alcohol (90 parts) until differentiation is completed. The sections are now placed on the slide and blotted with filter-paper, and cleared in oil of cajuput. Wash off the oil with benzin and mount in a solution of colophony in benzin; the cement is applied and is gently warmed in order to vaporize the benzin; if the benzin inflames, blow out the flame and continue the warming; finally, when the benzin has been expelled, apply a cover-glass.

In the hands of the author the following method has given better and more uniform results: Fix the tissues, which should be as fresh as possible, in mercury bichlorid solution (p. 49), embed in paraffin (p. 51), section, and cement to the slide in the usual way; remove the paraffin, wash in alcohol followed by water, and stain sections for from five to thirty minutes in the following solution:

Toluidin-blue,	1.5 gm.
Carbolic acid, 5 per cent. solution in water,	100.0 c.c.

This solution keeps indefinitely. After staining, wash the section well in water and differentiate in styrone (p. 68), Unna's glycerin-ether mixture (p. 68), acidulated water, or alcohol; wash with water again, quickly dehydrate in ordinary alcohol, and clear

in cedar oil. The chromophilic substance is stained a dark blue, the intensity of which depends on the extent to which the differentiation has been carried. (See Remarks on Staining, p. 63; also references given for Styrone and Glycerin Ether.)

In the great majority of instances the processes of the nerve cells that become axis-cylinders of nerves, in a short distance after passing from the cells, are enveloped in a sheathing of a peculiar substance, nearly related to fat, known as *myelin* or the *white substance of Schwann*. After this substance surrounds the axis-cylinder it is a matter of great difficulty to stain it so that it can be differentiated from the neighboring tissue. As the myelin sheath accompanies it almost to its termination, attention was directed to the staining of this covering rather than to the axis-cylinder itself; coloration of the myelin sheath is accomplished in a most beautiful manner by the method of Weigert or some modification of his process.

The Weigert-Kulchitzky-Wolters Method of Staining the Myelin Sheaths of Nerves.—(1) The tissues are hardened in Müller's fluid until they acquire a brown color; this takes generally from six weeks to three months. Dehydrate and embed in celloidin. (See p. 59.) (2) Sections are stained in the following solution for twenty-four hours in the incubator (37° C.):

Hematoxylin (crystals),	1 gm.
Absolute alcohol,	10 c.c.

Dissolve the hematoxylin in the alcohol and add 100 c.c. of a two per cent. solution of acetic acid in water. (3) The sections are removed and washed for a few moments in Müller's solution. (4) They are next differentiated in a ⅓ of 1 per cent. solution of potassium permanganate, freshly prepared, for from twenty to thirty seconds. (5) The sections are transferred to the following solution for final washing out:

Oxalic acid,	1 gm.
Potassium sulphite,	1 gm.
Distilled water,	200 c.c.

In a few seconds everything is decolorized except the myelin sheath, which becomes a blue-black color. The sections are now dehydrated in alcohol in the usual way, cleared in xylol or cedar oil, and mounted in balsam.

In addition to the purely nervous elements of the central nervous system, there is a supporting structure, as has been before remarked, known as the **neuroglia.** This consists of numerous small cells, termed *glia cells*, and tangled masses of *fibrils* that

closely surround the cells and the various nerve elements; it is not probable that these fibrils are really connected with the glia cells. The glia cells are seen after preparing tissues in the ordinary way, but the fibrils are brought out only by special methods, among which is that of Golgi. Better, however, is *Mallory's neuroglia method*, which is a *modification of Weigert's fibrin stain;* the steps in this process are as follows:

(1) The tissue must be absolutely fresh to get good results; pieces removed later than three hours after death do not give results at all satisfactory. Portions of the brain or cord are cut into thin slices and placed in a mixture of 10 parts of formalin and 90 parts of a saturated solution of picric acid in water. The tissue remains in this solution for eight days. (2) It is then transferred to a 5 per cent. solution of ammonium bichromate in water and placed in an incubator at 37° C. for six days, or at room-temperature for three or four weeks. The solution should be changed on the second day. (3) Place directly in ordinary alcohol. (4) Embed in celloidin. (See p. 59.) (5) Fasten section to the slides by ether vapor. (See p. 62.) (6) Stain for from fifteen to twenty minutes in a saturated solution of anilin oil in water (see p. 94) to which two per cent. of gentian-violet has been added. (7) Wash with normal salt solution. (8) Pour on some of the following solution, and let it remain for one minute:

Potassium iodid,	2 gm.
Iodin,	1 gm.
Water,	100 c.c.

(9) Wash with water. (10) Dry well by pressing filter-paper firmly on the section. (11) Decolorize in a mixture of equal parts of anilin oil and xylol. (12) Wash with xylol. (13) Balsam.

The nuclei and the neuroglia fibers are stained an intense blue; all other tissues, colorless, unless fibrin happens to be present, which is also stained blue.

The *white substance* consists of axis-cylinders covered by myelin, also united by neuroglia. The *gray matter* of the central nervous system is made up of ganglion cells and their processes, bound together by neuroglia. The ganglion cells of the gray substance show certain peculiarities in different situations; as examples of this may be cited the arrangements and especial characteristics of the cells of the gray matter of the cerebrum, of the cerebellum, and of the spinal cord. In the cerebral cortex the gray matter begins just beneath the pia. The outer layer of this contains only protoplasmic processes and neuroglia, and is

called the *molecular layer*. Just beneath there is a layer that, in addition to the foregoing, also exhibits many very small pyramidal ganglion cells. Beneath this is another layer, also resembling the first, but the ganglion cells are longer than in the layer last referred to. Still deeper, and forming the lowest layer of gray matter, is a fourth layer, in which the nerve cells are irregular in form, and are hence termed polymorphous. Most of these cells give off axis-cylinders of nerves.

The outer part of the gray matter of the cerebellar cortex is also termed the *molecular layer*. In it are two kinds of nerve cells—the small, occupying the outer part of the layer, and the *large* or *basket cells*, lying more deeply. Beneath the molecular layer is a very thin stratum, in which the *cells of Purkinje* lie. These cells are very large, and send off abundant protoplasmic processes; they are unique in that they are the only ganglion cells in the cerebellum giving off axis-cylinders that become nerves.

Beneath the molecular layer is a *granule layer* containing numerous cells, some of which are slightly larger than others. The nuclei of these cells stain intensely, and hence belong to the group of cells called karyochromes.

The anterior cornua in the spinal cord also contain numerous large multipolar ganglion cells. In the lower part of the dorsal and upper part of the lumbar cord a group of nerve cells lies in the inner part of the neck of the posterior horn—the *column of Clarke*. The neuroglia cells are very numerous immediately around the central canal of the cord, which area is often called the *substantia gelatinosa centralis*.

The arteries of the central nervous system are abundantly supplied with elastic tissue, the contractility of which is not apparently lost with age; for this reason it is thought that ordinarily the mind does not correspondingly fail along with the strength and other bodily functions in old age.

The nerves passing from the brain and cord consist of numerous bundles of nerve-fibers inclosed in a common sheath of fibrous tissue, called the *epineurium*. The individual bundles are surrounded by a sheath, continuous with the foregoing, termed the *perineurium*; the perineurium sends processes between the nerve-fibers, which support the blood-vessels, known as the *endoneurium*. Around each individual nerve-fiber there is a delicate sheath, known as the *primitive sheath*, within which is the myelin sheath surrounding the axis-cyl[illegible]. It should be remembered, however, that the myel[illegible] in the nerves of the sympathetic

absent in the cerebrospinal nerves. When the myelin sheath occurs, it is interrupted at regular intervals; such interruptions are known as the *constrictions* or *nodes of Ranvier;* at these points the axis-cylinder and the primitive sheath come directly in contact. When nerves branch, they always do so at these constrictions. Just before the nerve ends the myelin sheath terminates, and the axis-cylinder is continued onward inclosed only in its primitive sheath.

MALFORMATIONS OF THE BRAIN AND SPINAL CORD.

The brain and spinal cord take their origin from the formation and subsequent invagination and closing-over of a depression in the *superior germinal layer*, known as the *medullary groove*. After closing, this groove forms a cylindric canal, known as the *medullary tube* (*neural tube*), the walls of which are formed by the invaginated *epiblastic* tissues from the superior germinal layer just mentioned. This tube occupies the position in the embryo corresponding to that of the future spinal cord and brain. The cord is formed from the posterior part of the tube, while the brain is developed from three saccular dilatations, known as *vesicles*, which form toward its anterior end; the first and third of these vesicles are each later subdivided into two, making, in all, five vesicles, from which the different parts of the brain take their origin. The epiblastic tissues constituting the covering of the medullary tube especially multiply, so that the walls of the tube are greatly thickened and the developing cells become specialized into the peculiar component elements that go to make up the central nervous system. This thickening encroaches on the lumen of the tube, but a small canal in the center, and much larger cavities in the brain, persist throughout life; the former is called the *central canal of the cord*, and the latter are known as *ventricles*. These cavities are all lined by epithelial cells, which in early life are ciliated.

In normal development the medullary groove is entirely cut off from the superior germinal layer, from which it springs. It occasionally occurs that the groove is not closed, and a part or even all of it remains patent; under these circumstances neither the bony arches of the vertebræ nor the posterior and upper cranial bones develop in the situation where the groove fails to close. In these cases malformations of the brain or cord result, the character of which depends on the situation, kind, and extent of the areas of the groove not closed over. We possess no absolute knowledge as to the cause of these conditions.

Craniorachischisis Totalis.—When the entire medullary groove remains patent, neither the skull nor the vertebræ close posteriorly; the resulting condition is called craniorachischisis totalis. A fetus that at birth presents this malformation is found to have on the dorsal surface of its trunk a wide, shallow depression, uncovered by skin, occupying the median line, which, passing upward, becomes expanded over the posterior part of the head. In the median line of this fissure, flattened out over the bodies of the vertebræ, there are found varying amounts of a delicate, soft, and very vascular tissue, consisting of the rudiments of the brain and cord; in rare cases no nervous tissue can be demonstrated in this mass. In many cases, however, the anterior part of the brain is fairly well developed. The external surface of the fissure is covered by columnar epithelium, which is continuous on each side with the squamous epithelium of the skin, and corresponds to the epithelial lining of the central canal of the cord and the ventricles of the brain. Between the rudimentary nerve substance and the bodies of the vertebræ are the highly vascular tissues of the pia and arachnoid, and, still more deeply, a fibrous membrane—the dura; between the arachnoid and dura there is a space filled with fluid, which corresponds to the subdural space. In total craniorachischisis the eyes project prominently from the flattened skull, but generally neither they nor the nose are greatly displaced. The spinal column is always abnormally curved forward.

Much commoner than failure of the entire medullary tube to develop are limited defects restricted to small areas of either the cranial or spinal portions. These local anomalies can be more easily understood from an examination of the spinal malformations; and as they, in a way, lead up to the more complex but analogous conditions occurring in the brain, they will be first considered.

Rachischisis Totalis (Holorachischisis).—In case the entire spinal portion of the groove remains patent the condition that results is known as rachischisis totalis. With the exception of the fact that the brain is not involved, this condition differs in no way from craniorachischisis totalis, and a separate description is therefore unnecessary.

Rachischisis Partialis (Merorachischisis).—When only a part of the spinal portion of the medullary tube fails to close over, the resulting condition is called rachischisis partialis; this is most frequent in the sacrolumbar and cervical regions, but the intermediate parts are also occasionally affected. As in total rachischisis, the rudimentary spinal cord is exposed—owing to a

failure of development on the part of the vertebral arches—in the situations where the groove remains patent, and the anatomy of the condition is essentially that of the more pronounced malformations. The spinal cord in the affected area is spread out on the vertebral bodies, forming an irregular layer of soft, red, and very vascular tissue, which connects the two ends of the normal cord, or, in some instances, forms the termination of the cord below; in many cases, however, this intervening rudimentary substance is present to a very limited degree, or may even be entirely absent. When nervous structures are present, they are covered by columnar epithelial cells, and lie upon a membrane that corresponds to the pia of the normal cord. The edges of this pial membrane are usually exposed at the lateral margins of the spinal substance, and, therefore, intervene between the latter and the skin of the back. Near the upper or lower margin of the defective cord, or at both points, there is a small depression, which corresponds to the closed end of the central canal of the normal cord beyond. Between the pia, on which the undeveloped cord lies, and the bodies of the vertebræ are the arachnoid and dural membranes, with the intervening spaces filled with liquid, as in the normal vertebral canal.

Myelomeningocele.—When the condition just described exists in infants or children, especially if it be, as is generally the case, toward the lower end of the spinal column, the subarachnoid space frequently dilates as a result of the long-continued pressure of the fluid within on the delicate pia, which, with the rudimentary cord, forms the external wall of the cavity. In the beginning the structures just mentioned, with a few delicate strands of tissue from the arachnoid, form the entire outer wall of the tumor, but as the swelling increases the neighboring skin becomes a part of its external support. This condition is technically known as **myelomeningocele.** When the myelomeningocele is situated at the end of the cord, the tumor shows on its convex surface a slight depression, which corresponds to the closed end of the central canal of the cord previously referred to.

Meningocele.—This is another variety of malformation closely resembling in appearance the one just considered; it, however, differs from it, in that it appears not to depend on an abnormal development of the medullary tube, but is due to a deficiency of the bony wall of the vertebral column. Under these circumstances there is sometimes formed a saccular tumor, the walls of which are composed of the external layer of the

arachnoid and the dura, external to which are the soft parts covering the particular area involved. Meningocele is most frequently found in the sacral region, where defects in the vertebræ are most common. In rare instances the defect is in the body of the vertebræ, in which case the sac projects forward; it is thus possible for the tumor to protrude into the abdominal cavity.

Myelocystocele (Hydromyelocele).—When there are deficiencies in the vertebræ, saccular tumors are in rare instances developed having their origin in accumulations of fluid in the central canal of the cord. In their outward appearance they closely resemble meningocele, but, of course, differ in that the inner wall of the tumor is composed of the compressed substance of the cord. Myelocystocele in most instances occurs in connection with lateral clefts in the vertebræ, and defects in their bodies are also often present. Shortening of the trunk is a frequent consequence. When there is no defect in the vertebral column, the central canal is sometimes dilated as a result of increased amounts of fluid within (**salpingomyelus**; **hydromyelia**); the dilatation may be diffuse. Meningocele and myelocystocele sometimes occur together; the condition is known as **myelocystomeningocele.**

Spina bifida is the common clinical term employed for designating any of the foregoing conditions associated with the formation of tumor-like masses.

Malformations of the spinal cord without accompanying defects in the vertebræ are quite unusual, and are rarely of a pronounced character. However, the cord is sometimes abnormally short and slender (**micromyelia**), and occasionally exhibits partial duplications (**diastematomyelia**). Asymmetries also occur.

Defects in the nerve-roots are comparatively frequent.

Primary defective development of the nerve tracts has also been observed; this is of interest, in that it may become the starting-point of disease in later life.

An anomalous condition of the spinal cord is occasionally observed, known as **heterotopia**; in this condition the gray substance does not bear its normal relation to the white matter, but is more or less scattered through it.

The **malformations of the brain** in general correspond to those occurring in the cord; the causes, however, of the various defects are not so well understood. In addition to craniorachischisis, which has been described, there is no doubt that many of the other cerebral malformations owe their origin

to permanent patency of the medullary groove; it is equally clear that others result from fluids accumulating in the cranial cavity of the embryo, and causing rupture of the bony walls. There are doubtless also other causes that occasionally produce these conditions, the real nature of which, however, is largely a matter of conjecture.

Cranioschisis is a condition produced by the same cause as, and closely related to, craniorachischisis, and corresponds in the brain to rachischisis of the cord. Here, also, the cranial

FIG. 325.—SPINA BIFIDA.

vault is to a greater or less extent absent, and on the basal bones a reddish mass of tissue lies, which may contain rudimentary brain substance, or, more rarely, none at all (**anencephalia**). This reddish mass is covered by columnar epithelium, which becomes continuous with the surrounding skin, as in rachischisis. The base of the skull is very small, while the jaw and eyes project prominently, giving to the head a very characteristic appearance; for this reason it is sometimes spoken of as *cat-head* or *toad-head*.

It occasionally happens that one or more of the gyri fail in a

greater or less degree to develop, leaving, at the point, a depression that may extend to the ventricle. These cavities of the cerebral cortex are most common in the central and parietal lobes. They have received the name of **porencephalia.** Cavities very similar to these may occur in the cerebral cortex as the result of disease; such a condition is termed **pseudo-porencephalia.**

Circumscribed errors in development occur in the skull analogous to those that are seen in the spinal column, but differing from them in some minor details. They are most frequent in the median line, and in the majority of instances are situated in the posterior portion of the skull.

Encephalomeningocele corresponds to myelomeningocele; it consists of a saccular tumor of varying size projecting from the skull at some point—usually the occipital region. On section its walls are found to consist of the outer layer of the arachnoid, the dura, and the skin and a hernial projection of brain-substance, which at the apex of the tumor is closely adherent to the meningeal coverings, these being, in turn, firmly united to the skin; a small scar, or, sometimes, a minute mass of reddish tissue, representing the point where the medullary groove failed to close, will usually be found on the external surface of the skin, corresponding to the point of adhesion of the membranes below. More or less fluid is present in the sac, usually between the brain and the adjacent wall.

Meningocele.—Should brain-substance be entirely absent from such a saccular tumor as has just been described, the condition is called meningocele.

Encephalocele.—The term encephalocele is used to designate those saccular tumors springing from the skull that contain brain substance as well as the meninges, but no fluid. They are closely allied to the conditions previously referred to.

Accumulations of fluids not infrequently occur in the ventricles of the brain corresponding to myelocystocele, salpingocele, and hydromyelia; the condition is known as **internal congenital hydrocephalus.** This abnormality is, as a rule, not compatible with health or long life, but infants so afflicted not infrequently live for a number of years, and complete recovery sometimes occurs. When an infant, Thackeray is said to have been hydrocephalic. This condition is associated, when at all extreme, with enlargement of the skull, greatly interfering with the normal ossification of the bones composing it; in some instances the intracranial pressure becomes so great that rupture occurs, though death does not necessarily result. It has been mentioned that

some of the malformations of the brain are brought about by such a rupture occurring *in utero*.

Small portions of the ventricles of the brain are sometimes cut off by adhesions from the main cavities. When this happens, the part so cut off becomes greatly distended, as a result of accumulations of fluids within; portions of the fourth ventricle and the posterior horns of the lateral ventricles most frequently exhibit this abnormality. A like process sometimes occurs in the fifth ventricle.

Cyclopia (Synophthalmia).—When there is arrest of development in the anterior part of the brain, a malformation known as cyclopia sometimes occurs, mainly characterized by the fact that there is only one optic nerve, both eyes being fused into one organ that usually occupies a cavity in the center of the forehead; all the face-bones except the upper jaw may be absent. (See p. 552.) The nose often fails to develop; when present, it is malformed, and occupies a position above the eye. Sometimes the anterior portion of the brain fails to divide into two hemispheres, as is normally the case, and the ventricle may be so dilated that the brain has the appearance of a large cyst (**cyclocephalia**). In less severe forms of this condition the two eyes may be only partly fused, or may, without union of any kind, lie in the same cavity.

Arhinencephalia.—This condition, with the exception that the nose is always absent, and also the olfactory bulbs, is practically identical with cyclopia; it has been shown, however, that arhinencephalia may exist without very marked malformation of the eyes. This condition is accompanied by cyclocephalia; absence of olfactory nerves; fissure of the upper lip and palate; defective development of the intermaxillary bone and nasal septum; malformations of the heart, great vessels, and auricular appendages; umbilical hernia; supernumerary fingers and toes; and defects of the diaphragm.

Microcephaly. — This condition may be associated with arhinencephalia. It is characterized by the following peculiarities: the brain is very small; its convolutions are poorly marked off and much less numerous than usual; everything about the brain attests the fact that it is undeveloped; the skull is small and its bones exhibit many abnormalities of ossification, or numerous Wormian bones may be present. If any or all of the ventricles are dilated, the condition is known as **hydromicrocephaly.**

Partial hypoplasia of the brain may also occur. It is most common in the cerebrum and cerebellum, though it may involve

other parts of the central nervous system. If the gyri are abnormally small and numerous, the condition is called **microgyria.**

Hypertrophy of the brain may occur, but the condition is rare. Under these circumstances the normal elements present in the brain are to a greater or less extent increased in number.

Heterotopia of the gray matter is a condition analogous to that observed in the cord: the gray matter is present here and there in the white substance, giving it a mottled appearance.

DISEASES OF THE MEMBRANES OF THE BRAIN AND SPINAL CORD.

Diseases of the membranes of both the brain and cord will be considered together, for not only are they practically identical in their anatomy, and very closely related by continuity of surface, but they are affected alike in disease, and oftentimes simultaneously. As the dura may be diseased and the membrane that lies internal to it may be to all intents and purposes normal, and vice versa, it becomes necessary to consider their pathologic conditions separately.

THE DURA MATER.

Circulatory Disturbances.—*Active hyperemia* occurs in the dura in the first stages of inflammation. *Passive hyperemia* would be induced by obstruction, from any cause whatsoever, of the larger veins or sinuses. *Hemorrhages* are usually the result of injury, but may occur in scurvy, and, occasionally, in infectious diseases.

Inflammations of the dura, or pachymeningitis, may be acute or chronic, and suppurative, fibrinous, or productive in character.

Suppurative pachymeningitis is the most frequent variety of inflammation of the dura; it may be acute or chronic. It is, in the majority of instances, secondary to suppurative disease of the middle ear, but may occur after injury or disease of the skull or vertebræ; it is sometimes caused by the suppuration of thrombi in the various sinuses, and is rarely secondary to inflammations of the pia and arachnoid.

The membrane is swollen, owing to the presence of increased amounts of fluid, and is somewhat reddened. Microscopically, the tissues are found to contain many multinuclear leukocytes, swollen connective-tissue cells, and multitudes of bacteria.

Chronic internal pachymeningitis is a very peculiar variety of inflammation affecting the dura of the cranial cavity; its causes are not understood. The inner surface of the dura is alone involved, and in some instances the inflammation extends to the pia and arachnoid; the bones of the skull are sometimes diseased in the vicinity. Generally, the entire surface of the cranial dura is affected, though the condition is sometimes restricted to one or more small areas, on one or both sides of the brain. In the beginning stages of the disease there forms on the internal surface of the dura a thin false membrane, consisting of fibrin, in which are many connective-tissue cells and a few leukocytes. At a later stage the fibrinous mass is permeated by blood-vessels; these vessels very frequently rupture, giving rise to hemorrhage, and justifying the name **hemorrhagic pachymeningitis**, which is generally employed to designate this condition. The hemorrhages are usually small, but sometimes are sufficiently large to exert considerable pressure on the brain; when profuse, they produce tumor-like masses called hematomata. At a later stage more or less fibrous tissue is formed in the false membrane, and the condition assumes the form of a productive inflammation. Sometimes the false membrane is, in a manner, absorbed, but the fibrous tissue remains as a scar. If the condition be once set up, complete recovery probably never occurs—there being periods of improvement followed by exacerbations. The disease is very rarely seen outside of asylums for the insane.

Tuberculosis of the dura is secondary to tuberculosis of the inner membranes, or follows tuberculosis of the bones of the skull or vertebræ. The tubercles present the same nodular characteristics, with areas of caseation, that are seen in tuberculosis of other parts of the body.

Syphilis of the dura alone is quite rare. It occurs as local thickenings of the membrane, in which there are collections of lymphoid and plasma cells, and an increase in the amount of fibrous tissue; at a later stage calcareous deposits sometimes occur in these areas. The blood-vessels generally show evidence of endarteritis. Within the areas there may be small masses of caseous material.

Tumors.—*Spindle-celled sarcoma* is the most frequent tumor of the dura, but the other varieties of sarcoma are occasionally seen. *Endothelioma* is also sometimes found; these tumors may become quite large. *Psammoma*, *fibroma*, and *secondary carcinoma* sometimes occur; *osteoma* and *enchondroma* have been observed.

THE PIA AND ARACHNOID.

Circulatory Disturbances.—*Active hyperemia* is produced by any irritant acting on the membranes. It is, therefore, of course, always present in the beginning of inflammations.

Passive hyperemia is the result of thrombosis of any of the large intracranial vessels, and is also produced by tumors and exudations pressing upon and obstructing the veins. Under these conditions the hyperemia may be more or less localized. A more general condition of hyperemia of the passive kind is caused by obstructive diseases of the heart or lungs that interfere with the onward flow of the blood.

These abnormal states of the meninges are, of course, recognized by the fact that there is more blood present within their vessels than is normal. The recognition of these conditions, even post-mortem, is often difficult, for after death the blood gravitates to the most dependent situations. If, therefore, the head of the subject be placed lower than the body for any length of time, the brain, on section, presents an appearance of extreme congestion. This may also occur to a limited degree if the skull be opened before the other cavities of the body.

Anemia of the meninges occurs in general anemic conditions and when there is narrowing of the vessels that carry the blood into the parts. *Edema* of the brain occurs under those conditions in which the walls of the blood-vessels become so damaged that they permit the fluids of the blood to pass into the surrounding parts more rapidly than the lymphatics can remove them. It is most common in inflammations, and as a result of the pressure on the vessels by morbid growths. The condition is characterized by the presence of swelling, and on section more fluid exudes than is normally the case; the membranes have generally a translucent, gelatinous appearance. If the ventricular plexuses—which, it will be remembered, are but extensions of the pia—become inflamed or otherwise diseased in such a way as to cause increased permeability of the walls of the blood-vessels within them, it must follow that the quantity of fluids in the ventricles will be increased. This may cause distention and enlargement of the ventricles; the condition is called **acquired hydrocephalus.**

In this connection it may be remarked that in atrophy of the brain the space made vacant by the process may be filled with fluid. The condition is termed *hydrops ex vacuo.*

Inflammation of the pia and arachnoid is called **lepto-meningitis**, or simply **meningitis.** Like inflammations of the

dura, it may be *acute* or *chronic*, and *suppurative*, *fibrinous*, or *productive*; as in inflammations elsewhere, the acute forms are likely to be suppurative or fibrinous, or a combination of the two, while in the chronic forms fibrous tissue is produced, and the inflammation is consequently spoken of as productive. In a certain proportion of cases both the membranes of the brain and cord are affected, but more frequently the inflammation is confined to those of the cranial cavity; rarely, the diseased condition occurs only in the membranes of the cord. In the great majority of cases the disease may be looked upon as merely incidental, it being secondary to pathologic conditions in other parts of the body, or due to morbific influences that affect the body as a whole. The exception to this is the epidemic form, which is an entirely separate and distinct disease; this variety will therefore be considered separately. What we may term, for convenience, *incidental meningitis* may be divided into acute and chronic forms.

The acute form is more common in children than in adults. Investigations within recent years have shown that in quite a number of the diseases that predispose to meningitis the same micro-organism is responsible for both conditions. Belonging to this group are the meningeal inflammations occurring in connection with general tuberculosis, typhoid fever, erysipelas, pneumonia, and bubonic plague; it may result from septicemia, whether this comes from septic wounds, septic puerperal processes, the softening of clots, ulcerative endocarditis, malignant pustule, abscesses or other internal suppurations. To this list should be added septic processes in the vicinity of the brain, where there is extension of the inflammation into the meninges from contiguity of tissue, such as wounds of the scalp, erysipelas of the scalp or nasal cavities, glanders, actinomycosis, internal ear disease, septic inflammations of the eyes, caries of the cranial bones or vertebræ, and abscess of the brain or cord. Syphilis sometimes gives rise to meningitis.

Inflammation of the meninges also occurs in connection with such diseases as measles, scarlet fever, smallpox, and sunstroke. Excessive mental work is alleged sometimes to act as an exciting cause, but this is doubtful. Meningitis may also, of course, be the result of injuries to the skull. Lastly, in a certain proportion of cases meningitis occurs without antecedent disease. When it results as a complication of suppurative diseases, the same micro-organisms that give rise to the primary condition are usually found in the meninges; among these are the streptococcus pyogenes and the staphylococci pyogenes albus, aureus,

and citreus. There also have been found the bacillus pneumoniæ (Friedländer), the bacillus pyocyaneus, bacillus of glanders, bacillus of bubonic plague, bacillus communis coli, anthrax bacillus, and actinomyces. The pneumococcus is even more frequently found—occurring either in pure culture or mixed with other organisms in over one-half of all the cases.

In the tuberculous cases the bacillus of tuberculosis is, of course, always present.

Morbid Anatomy.—The inflammation may be limited to the meninges of the convexity of the brain, especially if the lesion

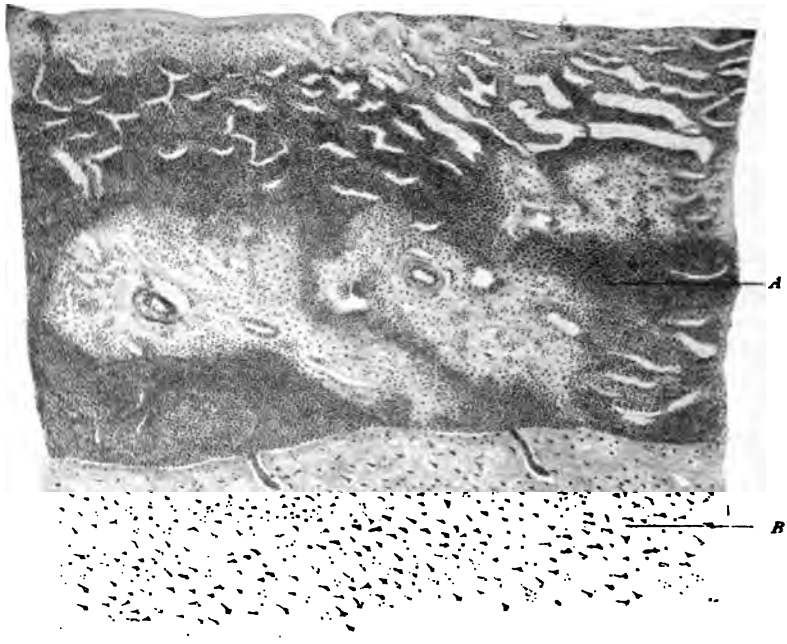


FIG. 32.—SECTION OF CEREBRAL CORTEX AND MENINGES FROM A CASE OF SUPPURATIVE MENINGITIS.

A. Pia arachnoid infiltrated with pus-cells. *B*. Normal brain-substance beneath.

be due to sunstroke or to local adjacent disease, and occasionally these parts are alone involved, when the process is the result of general conditions. The basal portion, except in tuberculosis, is very seldom alone affected. More frequently, evidences of the inflammatory process can be seen over the entire meninges. In the cord the inflammation is usually widespread.

The appearance of the membranes differ somewhat, depending upon whether the process be of a suppurative kind or not. In the former class of cases, which usually follow suppurative diseases, the membranes are distinctly reddened, swollen, and opaque, they are bathed in greenish, yellow, often fetid pus. The collections of pus are most numerous in the sulci of the brain, and may be seen around the nerve-roots. The inflammation sometimes spreads to the dura. The external surface of the brain may be reddened, and small areas of softening are occasionally seen. The lining membrane of the ventricle may also take on the inflammatory process; the fluids often greatly increase in the ventricles. In case suppuration does not occur the conditions are practically the same, with the exception that a serous or serofibrinous fluid, which may be slightly opaque, takes the place of the pus. On microscopic examination the vessels of the meninges are found distended with blood, and the swollen tissues are infiltrated with lymphoid cells and swollen connective-tissue cells; in the suppurative variety multitudes of multinuclear leukocytes are also found. The subjacent brain may be likewise infiltrated with leukocytes and lymphoid cells, and the nerve-fibers frequently show evidence of degenerative change. The same changes are found in the nerve-roots. Nerve degeneration, which will be again referred to, and more fully described, is evidenced in these situations by the white substance breaking up and forming irregular masses or droplets, which may or may not be united to one another by thin filaments of myelin. A part of the white substance undergoes a fatty change.

Method for Demonstrating Nerve Degenerations.—This may be done by the method of Weigert, already referred to. (See p. 746.) A better method is the following, which was devised by Marchi:

Place the specimen in Müller's fluid (p. 49), and allow it to remain eight days or longer. Remove, and cut into slices not more than three or four millimeters in thickness. Put these pieces in Marchi's mixture (see p. 244); let the tissue remain in this mixture for at least six or eight days. It is then removed, passed quickly through alcohol and alcohol and ether, and is embedded in celloidin. Examine the sections without staining. The fat in the degenerated nerves is stained black, while the normal nerves remain nearly colorless. This method depends on the fact that normal nerves lose their power of being colored by osmic acid after remaining in Müller's solution eight or ten days, while the fat still retains this power.

In **tubercular meningitis** the inflammatory phenomena vary

with the number of tubercles and the resistance offered by the tissue to the development of the process. Occasionally, only a few small nodules are found—generally in the basal meninges or in the fissure of Sylvius; under these circumstances there is no inflammation worth mentioning. In rare instances localized collections of such tubercles are found on the convexity of the brain, just in front of the fissure of Rolando; this variety of tuberculosis is called *meningitis en plaque*. Sometimes the tuberculous form is quite acute, and proves fatal in a few weeks; the exudate in these cases has a peculiar jelly-like appearance. The inflammatory phenomena are, however, never so marked as in the suppurative forms; distinct tubercles are not formed, or, if so, they are very minute. On microscopic examination the appearance is much like that of nonsuppurative meningitis. There are, however, more marked changes in the small blood-vessels than are usually found in the ordinary inflammations. The adventitiæ of the small arteries especially are in a large degree replaced by lymphoid and plasma cells, and a like condition of the intimæ is frequently found. A peculiar change in some of the vessels is that their intimæ are pushed inward some distance from the muscular coats, and the space thus produced is filled with fluids and a few lymphoid cells. This condition has also been noted by Ohlmacher in meningitis due to the typhoid bacillus. The collections of cells around the blood-vessels are beginning tubercles, for bacilli may be detected within them, and occasionally a giant cell is seen. In chronic cases well-formed tubercles with caseous centers are encountered. If the inflammatory process encroaches on the nervous tissues beneath, more or less degeneration results, and the parts are infiltrated with lymphoid cells.

Syphilis of the Meninges.—Gummata are sometimes found in the pia-arachnoid; they occur as flattened, pinkish or grayish nodules, which on section are often found to contain brokendown tissue in a caseous condition. Around these nodules there is always a considerable increase in the amount of fibrous tissue, and the blood-vessels show evidence of obliterative endarteritis. A general and more acute syphilitic inflammation of the meninges of both the brain and cord is sometimes encountered. The appearance of the meninges is much the same as in the acute tuberculous form, and on microscopic examination there is found to be but little difference in the histology of the two processes; however, there is evidence of obliterative endarteritis in the syphilitic form, and the peculiar giant cells of tuberculosis are absent. There is a chronic infantile meningitis, sometimes associated with syphilis. The membranes are opaque, thickened, and infiltrated with cells.

Chronic alcoholic meningitis results, as the name indicates, from the prolonged and excessive indulgence in alcoholic beverages. The meninges of the cerebral convexities are chiefly affected. The process is never very marked. The meninges are slightly opaque and thickened, especially over the sulci, and along the sides of some of the vessels there may be streaks of lymph. The microscopic appearances are those of nonsuppurative meningitis, though the inflammatory phenomena are less marked. Chronic inflammatory conditions of the meninges may also result from the pressure of tumors, foreign bodies, etc.

Cerebrospinal Meningitis.—This is an acute infectious disease, which generally occurs in epidemics. Though not limited to any age, it attacks most frequently individuals under twenty. There is good reason to believe that the disease is due to a small diplococcus discovered by Weichselbaum in 1887—the diplococcus intracellularis meningitidis.* (See p. 169.)

Morbid Anatomy.—In those cases in which death occurs within twenty-four hours the meninges are merely reddened; on microscopic examination a few lymphoid cells may be found in the vicinity of the vessels, and there may be here and there slight hemorrhages into the tissues.

In the later stages the membranes are intensely injected, and are covered by purulent, seropurulent, and fibrinopurulent exudations. In more advanced cases the membranes sometimes present the peculiar jelly-like appearance seen in tuberculous meningitis; this is due to the exudate becoming more fibrinous in character. The lesions are most marked at the base of the brain and along the posterior portion of the cord; nevertheless, all parts may be affected. On the cerebral convexities there is usually more exudate in the vicinity of the fissure of Rolando than elsewhere. On microscopic examination the meninges are found greatly swollen, containing many multinuclear leukocytes and enlarged connective-tissue cells; fibrin is also present. The blood-vessels are often thrombosed; around some of the vessels a few lymphoid cells are occasionally present. Within the pus-cells many of the specific micro-organisms are found. Councilman recommends the following method for demonstrating them: Stain the tissues, which have been fixed in corrosive sublimate, in a saturated solution of eosin in water, for an hour. Wash in

* During a recent epidemic of cerebrospinal meningitis in Boston the diplococcus intracellularis meningitidis was very thoroughly studied by Councilman, Mallory, and Wright, and much of the information in the present volume, both as regards the organism itself and the disease caused by it, was obtained from their excellent report on this subject.

water, stain one or two hours in Unna's alkaline methylene-blue (p. 67), diluted nine times with water. Wash off with water. Dehydrate in absolute alcohol, clear in xylol, and mount in xylol-balsam. The bacteria and the nuclei are stained blue, while the tissues in general are reddish. In the chronic cases the exudation is much less in amount, being confined to small areas, and consisting of degenerated pus-cells and granular detritus. The chronicity of the process results in the meninges becoming much thickened, from the formation of new fibrous tissue. In this tissue lymphoid and plasma cells are found.

In the brain and cord the vessels are injected, and the substance of both of these viscera is somewhat softened and edematous. Punctiform hemorrhages are occasionally seen. Both the cranial and spinal nerves are swollen and reddened.

Microscopic examination of the brain and cord shows the blood-vessels engorged with blood; the endothelial cells are swollen and increased in number, and mitotic figures are frequently found. The lesions in the brain-substance are generally not found below the molecular layer, though occasionally they extend much deeper—even entirely through the gray matter. The nervous tissues are more or less infiltrated with pus-cells, and the neuroglia cells become swollen and multiply. The ganglion cells are seen in all stages of degeneration, from slight irregularities in the chromophilic substance to its complete disappearance, and the final atrophy and disintegration of the entire cell. (Toluidin-blue or Nissl's method, see p. 745.) These changes are not so marked in the cord as in the brain. Many of the nerve-fibers in the brain, cord, and nerves show degenerative changes, demonstrable by the methods of Marchi or Weigert. (See pp. 761, 746.)

Tumors of the Pia-arachnoid.—*Sarcomata* are the most common of the new growths found in the meninges. They form rounded or flattened, soft, grayish or grayish-red tumors, which spread along the meninges and penetrate the brain-substance by means of the fibrous bands that pass inward from the pia. Microscopically, they show the usual peculiarities of the alveolar sarcomata. They are often referred to as *endotheliomata*. They occasionally occur as *angiosarcoma*, *myxosarcoma*, or *angiomyxosarcoma*; very rarely they are pigmented.

Rarer forms of tumors of the meninges are *myomata*, *fibromata*, *lipomata*, *chondromata*, *osteomata*, and *teratomata*. Secondary sarcomata and epitheliomata may also occur. *Dermoid cysts* are sometimes found. Cysts produced by *echinococci* and *cysticerci* are sometimes encountered.

THE BRAIN.

Circulatory Disturbances.—Anemia of the brain occurs as a result of general anemia, whether the latter be symptomatic or essential. The condition may also be brought about by obstructive diseases of the heart or lungs, and by the pressure of tumors on the vessels conveying the blood to the parts; tumors and collection of fluid in the brain may also so increase the intracranial pressure that the usual amount of blood can not enter the smaller vessels.

Morbid Anatomy.—The only macroscopic evidence of this condition is the pallor of the brain-substance. Microscopically, the smaller vessels contain but little blood; their walls may be thickened and hyaline.

Active hyperemia of the brain may be the result of overaction of the heart or of dilatation of the capillaries of the brain as a result of vasomotor disturbance; a sudden contraction of the arterioles of other parts of the body may also produce it. The hyperemia is local in cases when a large branch of an artery becomes suddenly obstructed, thus causing more blood to flow through the neighboring branches. The brain is actively congested in the beginning of inflammatory conditions, such, for example, as arise from sunstroke.

Morbid Anatomy.—The brain usually exhibits more or less redness on examination, but attention should again be called to the fact that the presence or absence of unusual quantities of blood in the brain or its meninges is to be regarded as furnishing anything but reliable evidence as to the condition preceding death, as the position in which the cadaver has been allowed to remain affects very greatly the quantity of blood in any particular part. If, however, the hyperemia be due to inflammation, the area involved will always show some redness if the condition be at all advanced. On microscopic examination the vessels may be found distended with blood, and if beginning inflammation be present, the usual evidences in the surrounding tissue will be apparent.

Passive hyperemia of the brain results from thrombosis of the larger venous sinuses, or pressure upon them by tumors, etc.; pressure on the superior vena cava or the innominate vein may also occasion it. It is produced in those diseases of the heart causing overfilling of the venous system. It is also observed, to a limited extent, during violent muscular efforts. It occurs to an extensive degree in death due to suffocation.

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Microscopically, the veins may be found dilated, and they not infrequently rupture; in long-standing cases blood pigment is sometimes found in the vessel-walls. Edema of the brain may result from either variety of hyperemia, but always occurs if the passive form persists for any length of time. In this condition the arachnoid spaces are dilated.

General Pathology of the Ganglion Cells.—Before considering those changes in the brain terminating in the formation of gross lesions of its substance it may be well to call attention to certain alterations in the ganglion cells that result from a large number of different morbific influences. These changes are, for the most part, of such a delicate character that they were not recognized by the older methods of research, and, hence, their very existence was not suspected until within the last few years. The exact nature of these changes is not clearly understood. They have been regarded as parenchymatous inflammations, occurring, as they always do, simultaneously with inflammatory conditions of the surrounding tissue; but as they have been observed in a large number of conditions to be clearly not inflammatory, it is very doubtful if they should be so considered. All these facts go to show that they are an invariable result of all influences, whatever their character, that act on the body in an injurious manner, and it would therefore seem much more logical to class them with the degenerations. Moreover, there is nothing in the peculiar character of the changes that could stamp them as being of an inflammatory nature.

Among the most interesting of all the more delicate changes that have been observed in ganglion cells are those described by Hodge as occurring in the ganglia and central nervous systems of animals as the result of subjecting them to long-continued electric stimulation, and to extreme fatigue. The following well-defined changes in the nerve-cells were observed: (1) *Nucleus:* Marked decrease in size. Change from smooth and rounded to a jagged irregular outline. Loss of open reticular appearance, with dark stains. (2) *Cell protoplasm:* Slight shrinkage in size with vacuolation for spinal ganglia; considerable shrinkage with enlargement of pericellular lymph-spaces for cells of cerebrum and cerebellum. Lessened power to stain or to reduce osmic acid. (3) For *cell-capsule*, when present: Decrease in size of nuclei. (4) Cells recover their normal condition if allowed to rest, but the process is slow.

These changes would seem to have a bearing on those neurasthenic states following worry and long-continued and unremitting attention to the details of business.

More pronounced changes occur in the various intoxications, in the acute diseases, and accompanying the various brain affections. Berkeley has recently shown that more or less well-defined alterations are produced in the ganglion cells of the central nervous system of animals, and even more pronounced changes in the dendrites and gemmulæ of these cells, as the result of serum-poisoning and recin-poisoning, and from the administration of alcohol.

Most marked changes in the chromophilic substance (toluidin-blue method) of the nerve-cells have been observed in a large number of different conditions in man, such as acute alcoholism, sunstroke, eclampsia, diabetes, uremic conditions, the anemias, all the infectious diseases, and in the auto-intoxications.

The change most frequently observed is fragmentation of the chromophilic masses of the cells, giving them the appearance of being smaller and more numerous than usual; if the disease-producing cause be severe, or if it continues to act, these bodies partly or completely disappear. In rare instances the bodies unite with each other, forming collections of chromophilic substance much larger than normal; all the bodies may unite, in which case the entire cell is stained almost uniformly. In all these conditions the quantity of pigment around the nucleus, if it existed primarily, may be greatly increased, or, if none is present, considerable quantities may form. The peculiarities of these pigment particles were referred to in describing the histology of ganglion cells. (See p. 743.) When the degenerate condition is pronounced, the nuclei show a tendency to pass from the center of the cell to its periphery, and it has even been asserted that they may be partly or completely extruded from the protoplasm. Simultaneously, the nuclei often show a tendency to mitotic division. The nuclei may swell, and several vacuoles often appear within a single nucleus.

The cell itself may appear much smaller than normal. In the early stages the protoplasmic processes show varicosities, and the gemmulæ are scanty or absent, but material obtained in the post-mortem room is rarely sufficiently fresh to permit the use of Golgi's method, by which alone these structures can be investigated.

In sections stained by the toluidin-blue method (p. 745) the processes and axis-cylinders of cells in severely diseased areas often appear broken off, giving the cell a smooth, rounded contour.

A degenerate cell would then generally appear under the microscope as a rounded body, with the protoplasm colorless or faintly stained, and the nucleus eccentrically placed.

It should not be forgotten that in bodies that have undergone postmortem change the nerve-cells exhibit changes that closely resemble those produced by disease. But at ordinary temperatures those changes will not be, as a rule, at all marked during the first twenty-four hours following death; if the body be frozen, changes may not occur even after many days. The alterations consist in a swelling of the cells, followed by the gradual loss in staining power of the chromophilic bodies and the appearance in the protoplasm of large vacuoles; the protoplasmic processes break off and the cell assumes an irregular outline. The nucleus swells also, and its outlines become blurred, and it may be dislodged and pass to one end of the cell; at a later period it entirely disappears. The nucleolus, last of all, swells, breaks up, and finally disappears.

Intracranial Hemorrhage.—Hemorrhage within the skull cavity may be in the membranes, in which case it is known as meningeal hemorrhage. This may again be divided according to its location: (1) *Extradural hemorrhage* is between the dura and the skull; when the hemorrhage is within the dura mater separating that membrane into layers, it is called (2) *intradural hemorrhage;* when the extravasated blood is beneath the dura, the condition is spoken of as (3) *subdural hemorrhage*. Such hemorrhages are practically always due to injury with or without fracture of the cranial bones. In hemorrhagic pachymeningitis (see p. 757) the hemorrhage is rarely profuse. The extended blood may, by pressure, influence the cerebral cortex, giving rise to degenerative and necrotic processes, and finally softening. It may undergo organization, either complete or partial, and persist in the form of cicatricial tissue. The most important form of intracranial hemorrhage is that occurring within the brain-substance.

Cerebral Hemorrhage.—Under cerebral hemorrhage is comprised all forms of hemorrhage into the brain cavity or its ventricles.

Etiology.—The most common form of cerebral hemorrhage is the variety that occurs in individuals who are almost always over forty years of age, and is due to an inflammatory condition of the walls of the smaller arteries in the brain, causing minute aneurysms, which subsequently rupture; this condition is commonly called **apoplexy.** Hemorrhage either from the meninges or brain-substance may result from violence, and may, of course, occur at any age. In addition to these causes, small punctiform hemorrhages into the brain are occasionally observed in diseases like syphilis and leukemia and in interstitial nephritis; these

hemorrhages are also found, as has been before mentioned, in meningitis and in hyperemia of the brain. Lastly, hemorrhage sometimes occurs from small vascular tumors.

Morbid Anatomy.—In that variety produced by disease of the blood-vessels the hemorrhage is nearly always solitary. According to Charcot and Bouchard, disease of the blood-vessels of the different parts of the brain occurs in the following order as regards frequency: Central ganglia, cortex, pons, cerebellum, centrum ovale, middle cerebellar peduncle, crus cerebri, and medulla oblongata; as might be expected, this order corresponds closely with the frequency of hemorrhage. One side of the brain is affected as often as the other. Though very rare, the hemorrhage occasionally occurs directly into the ventricles from the choroid plexuses, but the blood quite frequently finds its way into the ventricles by bursting through from the ganglia that form part of their walls. On cutting into an area of hemorrhage there is found toward the center a mass of clotted or semiclotted blood, merging on every side into the surrounding torn and lacerated tissues, which are often infiltrated with blood for quite a distance from the center of the lesion, thus giving the appearance of separate and distinct hemorrhagic areas in the vicinity. In rare instances almost the entire hemisphere into which the hemorrhage occurs may be destroyed. In the immediate area of the hemorrhage the nervous substance is, of course, entirely destroyed, and on microscopic examination there is found only the debris resulting from the breaking up of the normal structures of the part. If the patient does not succumb to the immediate attack, the extravasated blood begins quickly to undergo changes; it shrinks, and the color gradually fades until it finally is of a reddish-yellow hue. In the mean time the presence of the blood in the tissue results in an inflammatory condition of the neighboring structures, and in the formation of a fibrous capsule around the clot. In some cases a capsule is not produced, for the reason that some of the pyogenic organisms gain entrance to the part, and suppuration results; the condition then really becomes one of abscess. As the capsule forms around the clot, it gradually becomes smaller, as the result of absorption, but the newly formed fibrous tissue remains as a scar. In some instances the blood-clot undergoes liquefaction, and, becoming encapsulated, presents the characteristics of a cyst; it is thought that these cysts are sometimes absorbed, and that they are replaced by fibrous tissue. As a result of the formation and subsequent contraction of scar tissue in these processes the area in which the hemorrhage occurs is often markedly reduced in size. While the quantity of newly formed

cess in its substance commonly called **cerebral softening.** The most common causes of softening are thrombosis and embolism of the cerebral vessels, but, in addition to these, it may result from inflammations of the brain-substance, and it occasionally happens in old age without assignable cause. Thrombosis of the cerebral vessels is due most commonly to obliterative endarteritis and atheroma; as the former of these conditions is probably always syphilitic, and the latter frequently so, it is evident that syphilis plays an important rôle in the production of this condition. A vessel may also be occluded by pressure of tumors, masses of cicatricial tissue, etc. In peculiar states of blood accompanying child-birth, in acute diseases, and in cancer, gout, tuberculosis, and general malnutrition, simple thrombosis may occur. Embolism results most commonly from ulcerative diseases of the endocardium or its valves, but may arise from diseased conditions of the aorta or other large vessels; the plug sometimes comes from the lung, and may arise from aneurysms or morbid growths.

Morbid Anatomy.—When one of the cerebral vessels is occluded, the collateral circulation is rarely sufficient to cause anything like complete compensation; in the vast majority of instances the blood is practically excluded from the area supplied by the vessel involved, and, as a result, the tissue in the situation quickly dies. Thrombosis from syphilitic disease occurs more commonly in the larger vessels. Embolism of the middle cerebral arteries and their branches is more common than in the other vessels, and the vessels of the left side are more frequently plugged than those on the right. The immediate effect of the obstruction of a vessel, either as the result of thrombosis or embolism, is the arrest of the blood supply to the region supplied. As a result of this, the area involved appears abnormally white, but after twenty-four or thirty-six hours serum begins to collect in the part, pushing the nerve element apart and rendering the tissue edematous; the blood escapes from the walls of the affected vessels as a result of their degeneration and rupture, and the region involved assumes a yellowish or reddish color, depending on the quantity of blood effused. The nerve elements rapidly undergo degenerative changes, and break up into a mass of granular detritus; at this time appears a cell-like body, called the *compound granule corpuscle* in which are small particles of fat. In the course of a few weeks the blood pigment from the degenerate red cells begins to be absorbed, and as this process goes forward, the area, at first more or less of a reddish color, becomes yellowish, and finally white. These stages correspond

to the **red, yellow,** and **white softening** described by various authors. Red softening is most marked in the cortex, where the blood-vessels are numerous; yellow softening results from the red by degenerative changes in the blood pigment and by its absorption. White softening, in its purest form, generally occurs only in the white substance of the hemispheres. The area involved may be swollen and softer than the surrounding normal tissue, but oftentimes it differs but little from the neighboring normal substance.

In the early stages inflammatory reaction on the part of the surrounding tissue is evidenced by an increase of the neuroglia cells, and a few leukocytes from the normal blood-vessels in the vicinity are thrown out. In white softening particles from the diseased region show, when examined under the microscope, a *granular detritus, nuclei from the neuroglia, compound granule bodies*, and, at a late stage, *corpora amylacea*.

The changes produced in the nerve-fibers passing through the diseased area are the same as those that occur after hemorrhage.

If the softened areas are infected by any of the putrefactive or pyogenic bacteria, changes result that correspond to the peculiar micro-organism present. If the results of the occlusion do not earlier prove fatal, in the course of months or years the affected area may become encapsulated, and, if the contents be absorbed, a dense mass of fibrous tissue may entirely replace it. It sometimes happens that the solid parts alone are absorbed from the softened tissue, and a cyst results.

An examination of the vessels of a brain in which thrombosis has occurred shows the presence of an obliterative endarteritis or atheromatous disease. In the former condition the vessels will exhibit hard, nodular swellings along their course, which are the result of an increase in the thickness of their walls, and are never aneurysmal in character. The microscopic changes consist of a great increase in the amount of fibrous tissue in the inner coats of the vessels, and an alteration of the same character may be present in the outer coats. The intimæ so thicken that the lumina of the vessels are greatly reduced in size. At the point where the obstruction producing the softening has occurred, the decrease in caliber of the vessel is so great that a thrombus has been produced.

In case the vessels are atheromatous there will be found some thickening of the inner coats, and subsequent fatty degeneration with the possible formation of ulcers or calcareous plates resembling those that are often found in other vessels so

diseased. The obliterative change results in this case by the building up of a fibrinous plug from an ulcer, or the formation of like obstructions from the narrowing of the lumina of the affected vessels.

Thrombosis of the veins and sinuses is a condition sometimes encountered ; it may result from an altered condition of the circulating blood or from diseased conditions of structures in the vicinity of the vessels. Among the former are the blood states resulting from long-continued diarrhea, suppuration of any kind, acute specific diseases, and diseases of the lung ; it also occurs in the puerperal state and during the course of cancer. The condition is especially frequent in children.

Belonging to the class of abnormal conditions that produce thrombosis by their proximity to the veins or sinuses are injury or diseases of the bones of the skull, internal ear diseases, meningitis, tumors, erysipelas, carbuncle, and the presence of foreign bodies.

Morbid Anatomy.—In the great majority of instances the clot is situated in the superior longitudinal sinus ; this is probably in a measure due to the fact that the veins empty into it in a forward direction, and the current of the entering blood is therefore opposed to the course of that of the blood in the sinus, and, as a consequence, its circulation is feeble. The obstruction causes intense congestion in the blood-vessels supplying the occluded sinus, and edema in the area involved ; this congested condition of the vessels may lead to the rupture of the smaller ones, so that many minute areas of hemorrhage are often observed. Softening of the cerebral tissues occurs in the vicinity of the edematous and hemorrhagic spots. Within the vessel involved there may be found a clot, limited to one part or occupying its entire extent, at first dark and soft, but later becoming harder and more or less laminated, as a result of the deposition of successive layers of fibrin.

Infantile hemiplegia is a condition the pathology of which is not clearly established, but there is much evidence to show that it is the result of vascular obstruction. It occurs in children, following the acute infectious diseases.

Inflammations of the brain (cerebritis, encephalitis), like inflammations elsewhere, may be acute or chronic ; in addition, they may be simple, hemorrhagic, purulent, or productive.

Acute Inflammations.—The classification of acute inflammations of the brain is at the present time, unfortunately, in a state of great confusion. Authorities generally divide these inflammations into the following varieties : (1) **Acute encepha-**

litis, the result of injury; (2) **simple acute f** (hematogenous or insular), the result of th diseases; (3) **acute hemorrhagic encephalit purative encephalitis.**

It is obvious that at the time an injury occ a strong probability that the wound will be some micro-organism, and to the results of the will be quickly added the effects resulting fro the particular infectious agent introduced, and process is accordingly modified; again, nothin curate than merely to say an encephalitis occur tious or septic process, since the peculiarities duced would vary as widely as the diseases fr their origin. Even the term suppurative encep scientific, as there are many infectious agents c a process of this kind. As much as this con be deplored, in the present state of our know haps do no better than to follow the classificat with the exception only that all those inflan abscess, of a suppurative character will be i head.

The peculiarities of an inflammation the re of course, depend on the situation, kind, wound. If no infective agent be added, the the alterations following hemorrhage. Th in the vicinity of the injury is destroyed, an less inflammatory infiltration of cells into th wall may ultimately form around the diseased quent changes in the softened tissue and the ations ensuing are identical with those th rhage.

Simple acute focal encephalitis is a con exciting cause of the inflammation probably brain by means of the circulation. It may c with any of the infectious diseases, such as fever, diphtheria, and rabies; it sometimes re tism, and may follow sunstroke.

Etiology.—In some cases the lesion is due organism that gives rise to the disease in con it occurs, and in other instances the general predisposing cause, producing such a lowered on the part of the tissues of the brain th agents that happen to gain entrance to the culty in lodging and in producing the pe

occasion. It is not impossible, also, that the soluble poisons that are manufactured in the body in some infectious diseases may act directly upon the brain tissues as irritants.

Morbid Anatomy.—The lesions are generally scattered throughout the brain-substance as small foci, which may or may not be macroscopically perceptible. When large enough to be seen, they generally present a red appearance, and are softer than the neighboring nerve tissue. The areas are usually considerably redder than those of simple softening, this being due to the dilatation of the vessels in and around the diseased region, and to more or less extravasation of blood into the part. For the foregoing reasons inflammation of the brain was long confounded with softening, with which it presents many points in common. At a later stage, indeed, it may be impossible to distinguish between them, for the extravasated blood is gradually absorbed, or its coloring-matter so modified that the area becomes pale. In the stage of acute inflammation sections, when examined microscopically, show distention of the blood-vessels, small focal hemorrhages, and accumulations of lymphoid cells around the vessels. At a later stage there are many larger cells in the part that appear to be enlarged connective-tissue or neuroglia cells; there are also many plasma cells. The nerve cells and nerve-fibers undergo degenerative changes. If the area be small, it is not improbable that practical restitution to its normal condition may occur; but if larger, the most favorable result that can be looked for is the formation of a small scar, which replaces the tissue involved.

Acute hemorrhagic cerebritis is a rare affection, the cause of which is not known. The centrum ovale is said to be the part of the brain principally involved; it is softened, of a pinkish color, and shows numerous minute hemorrhages. The pia is also injected. The blood-vessels of the white substance are seen to be distended with blood when examined microscopically, and there are slight evidences of degeneration of the nerve-fibers in this situation. Hemorrhagic foci are frequent. The nerve cells of the cortex are normal.

Suppurative Cerebritis.—By far the most frequent and important of all the inflammatory conditions affecting the brain are those of a suppurative character. The disease may occur as a complication of any acute infective processes, such as erysipelas, pneumonia, cerebrospinal meningitis, poliomyelitis of the cord, and scarlet fever. It is occasionally seen in conditions accompanied by the presence of pyogenic cocci in the circulating media of the body; it may also occur in pyemia, septicemia, endocarditis, and

suppurative of distant parts. But at the present time more common than either of these causes is the direct extension of suppurating processes to the brain-substance from neighboring parts such as occurs in middle ear disease, chronic diseases of the nose, caries of the bones of the skull, and suppurative diseases of the meninges.

Etiology.—The most frequent organisms present in these conditions are the streptococcus pyogenes, the staphylococcus pyogenes albus, aureus, and citreus, and the bacillus pyocyaneus. Actinomyces are also occasionally present; the oidium albicans has been found, and other organisms have been occasionally observed.

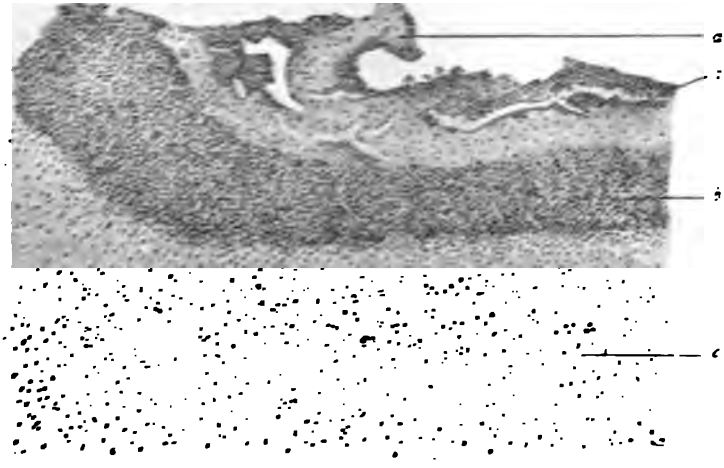

FIG. 91.—SECTION OF HUMAN BRAIN INCLUDING WALL OF CEREBELLAR ABSCESS.

a, a. Pus-cavity of abscess, containing pus-cells and granular detritus. *b.* Wall containing reparative elements. *c.* More or less normal brain-substance. (Green.)

Morbid Anatomy.—When the organisms producing the disease enter the brain by means of the circulation, numerous minute foci of inflammation usually occur; macroscopically, these resemble in every way the areas found in the simple acute form of cerebritis. When the infection comes from neighboring structures, it generally extends by continuity of surface to one part of the brain alone, and there occurs, as a consequence, only a localized inflammation at the infected point. When the diseased area is extensive, it is commonly called **cerebral** or **cerebellar abscess**. The cerebrum is diseased about four times as frequently as all the other parts together; next to the cerebrum the cerebellum

is most frequently affected. Within the diseased areas there is found a collection of yellowish or greenish, often fetid, pus, which, in addition to multinuclear leukocytes, contains the granular debris resulting from the breaking down of the nervous structure, and from multitudes of bacteria. The walls of the abscesses are irregular; often there are several abscesses near one another, connected by small sinuses. The surrounding tissue is swollen and pinkish in color; if the abscess be old, it is not infrequently surrounded by a more or less well-defined capsule of fibrous tissue.

Microscopically, the walls of the abscesses show degenerating nerve cells and nerve-fibers, an increase in the neuroglia cells, and infiltrating these areas of breaking-down tissue are multitudes of multinuclear leukocytes (pus-cells), which come from the surrounding engorged blood-vessels; enlarged connective-tissue cells, lymphocytes, and, especially if the process be subacute or chronic, numerous plasma cells are also found. The capsules of very old abscesses sometimes undergo calcareous change, and, in rare instances, the contents may do likewise.

Chronic Encephalitis.—But little is known of the chronic inflammatory conditions affecting the brain-substance alone, such lesions being apparently very rare. It is, however, quite conceivable—and even probable—that acute inflammatory processes, especially those of a nonsuppurative character, may in some instances become subacute or chronic. Cases have been recorded when there was postmortem evidence of such conditions, but it was impossible to say whether the cerebritis began as a chronic process or followed an acute inflammation. The macroscopic changes are slight or wanting in chronic cerebral inflammations, but microscopically there are evidences of slight inflammation, and sometimes small areas in which there is an increased amount of newly formed fibrous tissue.

Chronic Meningo-encephalitis.—This is a disease characterized by chronic inflammation of the brain-substance and meninges, giving rise to gradual impairment of the mind and to general paralysis; the condition is known clinically as **dementia paralytica.**

The disease seems to have some connection with syphilis, since in about seventy-five per cent. of all cases there is a history of an antecedent attack of this affection; traumatism, lead-poisoning, alcoholism, and prolonged mental strain have also been thought to be predisposing causes.

Morbid Anatomy.—The lesions observed in this affection have varied considerably, but those most commonly noticed are

atrophy, especially of the frontal lobes of the cerebrum, thickening of the dura, with the formation in some cases of a membrane on its inner surface, and thickening and opacity of the pia, which is adherent to the brain-substance below.

Microscopically, there are found small collections of lymphoid cells around the blood-vessels and more or less thickening of their adventitiæ. There is destruction of many nerve cells of the cortex, and, as a consequence, degeneration of the nerves that pass from them; these degenerations may be traced downward through the brain and cord. The tangential nerve-fibers lying in the molecular layer are, in severe cases, almost entirely destroyed. The protoplasmic processes of these cells are similarly affected. Along with these changes there is considerable formation of fibrous tissue in and around the processes passing into the brain from the pia. The neuroglia cells are greatly increased in number, and the neuroglia fibers may be thickened. The membranes show the usual microscopic evidences of chronic inflammation. The nerve cells of the cord show marked degenerative changes. The meninges of the cord are also much thickened; these changes are especially marked in the posterior portion of the cervical and dorsal cord, giving rise to pressure on the sensory nerve-roots, and thereby causing, oftentimes, much pain.

Syphilis of the brain is a rare affection; it may be manifested as a localized point of inflammation, producing a gumma, or in more or less wide-spread disease of the blood-vessels. The condition is always chronic. The gumma may be primarily located in the brain, but begins more commonly in the pia, and subsequently invades the brain-substance. These tumors are most common in the cerebrum. In the earlier stages a gumma presents a grayish or reddish-gray appearance, and is very firm in consistence and of an irregular outline; the growing surface has generally a gelatinous appearance. Later, small caseous nodules appear within the tumor; these nodules are separated from one another by bands of practically normal fibrous tissue. Under the microscope the gummata are found to consist of fibrous tissue, containing here and there small collections of lymphoid and plasma cells, in addition to the connective-tissue cells, which are scattered throughout the fibrous mass. The caseous spots consist of the granular debris resulting from the breaking down of the tissues of the part.

Tuberculosis of the Brain.—Coincident with the eruption of miliary tubercles in the meninges, lesions of the same character may be produced in the brain-substance; the cortical por-

tions are most frequently affected, though in some instances the deeper parts are also diseased. These miliary tubercles are gray or yellowish-white, and are softened in the center; hemorrhages sometimes occur around them. They are, of course, surrounded by an area of inflammatory tissue. These softened areas may coalesce, and much larger tubercles result. However, the large solitary tubercles generally occur as a result of the fact that but few tubercles are present, and the disease consequently runs a very protracted course, and each lesion has sufficient time to become large. These large tubercles resemble the smaller ones, but may become infected by pyogenic organisms, and as a consequence their contents sometimes become puriform; they are most common in the cerebellum. Microscopically, the tubercles of the central nervous system in every way resemble those occurring elsewhere.

Multiple Sclerosis of the Brain (Insular Sclerosis).—In this disease there occurs throughout the entire central nervous system areas in which the neuroglia is greatly increased in amount and the individual fibers are thickened and probably elongated. As the neuroglia corresponds to the fibrous tissue of other parts of the body, its hyperplastic condition in these instances may be looked upon as analogous to the fibrosis occurring in the kidney, liver, and other organs, under certain circumstances. These sclerotic changes may also be compared to those tumors of the central nervous system called *gliomata*, as in both instances the tissue of which the new formation consists is hyperplastic neuroglia; indeed, it can not be said that there is any sharp line of distinction between the two conditions—the two bearing exactly the same relation to each other that newly formed fibrous tissue in organs bears to the fibromata. The process, which is a very chronic one, often follows such diseases as malarial and typhoid fevers. The sclerotic areas vary much in size, some being only microscopic and others involving an entire lobe of the brain or including the spinal cord. In the white substance the areas of sclerosis, when sufficiently large, may be detected by their pinkish color, and by being considerably harder than the neighboring normal brain-substance; in the gray substance they are so near the color of the normal tissue that it is very difficult to distinguish them. In some cases the neuroglia just beneath the epithelial lining of the ventricles becomes hyperplastic, and the resulting condition is called **ependymal sclerosis.** The sclerosis may be diffuse, giving rise to a condition of uniform thickening, or it may occur in many minute circumscribed areas; the former variety of the

disease is called **smooth**, and the latter **granular ependymal sclerosis.** There is a form of sclerotic change known as **lobar sclerosis,** affecting one or more lobes of the brain, and sometimes the entire brain. The condition seems to have, in the beginning, some relation to the cerebral blood supply, as the lesion nearly always corresponds to the distribution of some artery. The entire region involved is very hard, the gyri are depressed, and the pia is adherent. Secondary degenerations are more pronounced in this form than in the other varieties.

Microscopically, the sclerosed area is found to be composed of hypertrophic or hyperplastic neuroglia fibers (demonstrable by the method of Mallory, see p. 747), and the neuroglia cells are also greatly increased. The nervous elements show more or less evidence of degenerative changes; the myelin sheaths of the nerves are largely destroyed, but, strange to say, the axis-cylinders do not exhibit, as a rule, marked alterations. The morbid changes are more pronounced around the small blood-vessels, the walls of which are usually thickened and frequently show more or less hyaline transformation. Compound granule bodies are often found in sclerosed areas. Other bodies, the result of degenerative change, are also frequently encountered in these lesions—namely, the corpora amylacea. They are rounded or oval bodies, generally somewhat larger than nerve cells, containing no nuclei, and staining brown with iodin, and a dark-blue color with toluidin-blue.

Tumors of the Brain.—Probably the most frequent cerebral tumor is a new growth, peculiar to the central nervous system, called *glioma.* The tumor is usually found in the cortical portion of the cerebrum, and does not, as a rule, protrude notably beyond the surface. On section it is found to consist of a gray or grayish-red substance, which may show whitish spots and hemorrhagic foci; some parts of the tumor are not uncommonly of a gelatinous consistency. Blood may be extravasated into the tumor to such an extent that it has the appearance of a massive hemorrhage into the brain-substance. It sometimes happens that the brain-substance in the vicinity of the tumor is more or less softened as a result of the pressure exerted by it.

Microscopically, these tumors consist of hyperplastic neuroglia; there is an enormous increase in the number of the glia cells, and the neuroglia fibers around them are thicker than normal and are greatly increased in number. In the center of the tumor neither nerve cells nor axis-cylinders are found, but if the tumor gradually merges into the surrounding nervous sub-

stance, as it not infrequently does, the edges of the tumor will contain these elements. The blood-vessels are usually very large and numerous; their walls often show hyaline degeneration, and the outer coats may be thickened.

If the tumor contains nerve cells and nerve-fibers, it is called *ganglionic neuroglioma.* If these be present in the white matter of the convolution or in the centrum ovale, they also contain nerve cells. They greatly resemble the simple glioma, and, with the exception that they contain, in addition to the neuroglia, the other elements of normal nervous substance in small quantity, they are identical. (See Glioma, p. 317.) The new growth may, to a certain extent, present the appearance of *sarcoma;* under these circumstances the tumor is a mixed one, and may be called a *gliosarcoma.* Gliomatous tumors appear to owe their origin to defects in development.

Sarcomata of the brain occur nearly as often as the gliomata. The tumors show the usual tendency to remain, in a measure, distinct from the normal structure of the part, though to a varying degree they infiltrate the surrounding tissues, especially the meninges. The meninges in the vicinity are often inflamed, and the adjacent nerve substance is usually more or less softened. Within the tumors hemorrhages and softening often occur. In certain of these the component parts become calcified, and the tumor is called a *psammoma.*

Angiomata of the brain sometimes occur; the tumors are quite small. They appear as small reddened areas. These tumors are probably congenital. *Fibromata* are very rare cerebral tumors. *Osteomata, lipomata,* and *cholesteomata* are occasionally seen. *Dermoid cysts* are sometimes found in the brain. *Carcinomata* are usually secondary; they resemble the peculiar variety of tumor from which they originate. *Primary carcinoma* may, however, occur, beginning in the epithelial cells of the ventricles. Secondary sarcomata are also sometimes observed.

The *cysticercus* and *echinococcus* are sometimes encountered in the brain.

Diseases of the Pituitary Body.—Enlargement of this body has frequently been observed in acromegaly (see p. 712); whether this be an effect or, as some maintain, the cause of the disease, has not as yet been determined. **Tuberculosis** and **gummata** are occasionally found in the *pituitary body.* The organ is rarely the seat of tumors. The most common of these are *adenomata,* which are made up of the hyperplastic follicles of the anterior lobe of the body. *Carcinomata, sarcomata, lipomata,* and *teratomata* have been observed.

Diseases of the Pineal Gland.—This body is very rarely the seat of primary disease. The most frequent alteration is an increase in the quantity of the *calcareous material* contained within it, and *cystic degeneration* is sometimes encountered. Tumors are very rare.

Diseases of the Larger Blood-vessels of the Cranium.—The great vessels that are at the base of the brain not infrequently become diseased.

The most frequent change observed is *atheromatous disease* of their walls. (See p. 515.) *Aneurysms* are not common, but are occasionally encountered.

Syphilitic endarteritis, already referred to in the articles on cerebral softening, sometimes affects the larger vessels outside the brain.

THE SPINAL CORD.*

Circulatory Disturbances.—*Anemia of the cord* occurs under the same circumstances that give rise to a like condition of the brain; exhausting hemorrhages, chlorosis, pernicious anemia, leukemia, and all of those diseases accompanied by lessened richness of the blood may cause the condition. The affected cord is paler than normal on removal, but the warning given in connection with hyperemia and anemia of the brain (see p. 765) applies with equal force here. *Active hyperemia of the cord* probably occurs only in the beginning of inflammation; it is certainly the case that we know nothing of hyperemia from other causes. Passive hyperemia may result from the recumbent posture if the individual be very weak. The cord would probably appear, under those circumstances, of a darker color than normal.

Hemorrhages into the cord are usually the result of the rupture of a blood-vessel from injury; this is especially the case if the hemorrhage be at all large. Minute hemorrhages sometimes occur into the substance of the spinal cord during acute disease; the blood may be extravasated into the central canal of the cord. The condition is spoken of as **hematomyelia.** It not infrequently occurs in that condition of dilatation of the central canal of the cord called *syringomyelia.*

Hemorrhage into the cord is followed by those degenerative changes described in the article on cerebral hemorrhage, and to which the reader is referred for further information. Degenerative changes in the nerve tracts that are injured may be traced to the termination of the nerves composing them.

* For minute anatomy see Histology of the Nervous System, p. 742.

These secondary degenerations will be more fully considered in the paragraphs on myelitis.

Myelitis or Inflammation of the Cord.—The disease may be *acute*, *subacute*, or *chronic*, depending on the cause. The acute and subacute forms may become chronic. There are several varieties of myelitis that show sufficiently distinctive features to merit separate description, but the form meant when the term myelitis is used without qualification will be first considered.

Perhaps the most frequent cause of myelitis is injury to the cord; to this group probably belong those cases following over-exertion and strain. Closely related to these are those inflammations, always more or less chronic, that are the result of the long-continued pressure of tumors, aneurysms, and cysts, and of the compression exerted by deformed vertebræ in caries of these bones.

Myelitis is also secondary to inflammations of the pia-arachnoid; it is, therefore, present in cerebrospinal meningitis, tubercular meningitis, etc. In such conditions as pyemia, septicemia, and other diseases when bacteria are present in the blood myelitis occasionally occurs; it is usually of a suppurative character, and is accompanied by a like process in the cerebral tissues. To this class probably belong those inflammations of the cord that follow smallpox, rheumatism, typhoid fever, and typhus fever. Sexual excesses, the suppression of the menses, and cold are supposed sometimes to occasion the disease. Syphilis and alcoholism are frequent causes of the chronic form.

Morbid Anatomy.—Both the white and gray matter may be affected. If the white substance be alone attacked, the disease is called **leukomyelitis**; if the inflammation be confined to the gray matter, the condition is termed **poliomyelitis.** The entire thickness of the cord may be diseased, in which case the affection is called **transverse myelitis.** If an extensive area be involved, the myelitis is said to be *diffuse;* if a small area alone of the cord be the seat of the disease, the condition is termed *focal myelitis;* if there should be many foci of inflammation, it is known as *disseminated myelitis.* Inflammation just around the central canal and extending more or less into the surrounding gray substance is called *central myelitis;* the anterior cornua may be also affected without disease in other parts of the gray matter.

On examination, the meninges in the vicinity of the diseased area are found to exhibit more or less evidence of inflammation. The cord may be swollen and softened, and on section presents a reddish appearance. If the inflammation be of an intense

character, the substance of the cord is almost of a creamy consistence; and if the amount of blood extravasated into it be considerable, the diseased area is said to be in a state of *red softening*. At a later period the pigment of effused blood undergoes changes, so that the softened tissues become yellow, and finally white, and the last two conditions are therefore called *yellow* and *white softening* respectively. If the disease be subacute or chronic, the cord may be either of a normal, increased, or diminished consistence; it usually presents a grayish appearance, as a result of an increase of the neuroglia; late in the disease small cavities in the affected area are occasionally encountered.

Microscopically, the blood-vessels are found to be greatly dilated in the acute forms, and there is often much blood extravasated into the affected tissues. The myelin sheaths of the nerves swell and become nodose, exhibiting here and there small areas of fatty degeneration; the axis-cylinders swell, become granular, and finally disintegrate. The nerve cells also show fatty change; they are vacuolated, the chromophilic substance no longer stains, and, finally, they disintegrate. The glia cells may undergo but little change, though they are usually somewhat swollen and increased in number. As the process grows older, and if it be pronounced, there remains of the original nerve elements scarcely more than fragments; compound granule cells may appear in considerable numbers. If the diseased tissues contain blood, many cells, called pigment granule cells, may be seen containing the pigments of the disintegrating blood. At a later period the granular detritus resulting from destruction of the nervous elements disappears, connective-tissue cells make their appearance, more or less connective tissue is produced, and the neuroglia fibers greatly increase. Corpora amylacea often form in the tissues as the process becomes old.

Secondary degenerations of the columns of the cord result from myelitis; the nature and extent of these depend on the situation and extent of the primary lesion in the cord. From the lesion, whatever its character, the degeneration proceeds along the nerve-fibers in the same direction in which the nervous impulses were carried before the injury occurred; the reason of this is that the axis-cylinders, being really part of the nerve cells from which they take their origin, are no longer properly nourished after being separated from the body of the cells. Lesions of the cord, therefore, cause descending degeneration in motor fibers and ascending degeneration in those of a sensory character.

The alterations that occur in the fibers are in every way similar to the degenerative changes following lesions in the cere-

brum, and for a description of which the reader is referred to the article dealing with this subject in connection with hemorrhage of the brain. (See p. 768.)

Acute ascending paralysis (*Landry's paralysis*) is a disease that, in the light of recent research, should be classed among the inflammatory diseases of the cord.

The cord shows no gross evidence of disease other than some redness of the gray matter and occasional hemorrhagic areas in its substance.

Microscopically, the gray matter of the cord, medulla, pons, cerebrum, and cerebellum exhibit the usual changes of beginning inflammation: The vessels are distended with blood, and around many of them are collections of lymphoid cells; the nerve cells show the alterations usual in inflammation; the white matter may be slightly, but evidently only secondarily, affected. Inflammatory changes have been observed in the nerve-roots.

Acute poliomyelitis is thought to be due to the same general causes that are believed to give rise to the ordinary forms of inflammation of the cord, but there are facts concerning it that would seem to indicate that it is a distinct disease—the result of some morbific agency having a predilection for this particular part of the nervous system. Among such facts may be mentioned that the disease frequently occurs without any apparent cause, and that it affects children almost exclusively —the period of life at which it comes on being usually about that of the first dentition. In support of the view that it is due to a specific disease-producing cause is the recent discovery of the micrococcus intracellularis in the tissues of the cord in the acute stages of the affection.

Morbid Anatomy.—If the disease be very severe, the meninges in the vicinity may be slightly reddened. On section the gray matter in one or both of the anterior cornua is redder than usual, and, if the disease be of a severe type and somewhat advanced, the tissues in this situation are considerably softer than usual. After the acute stages have passed the affected area will be somewhat more dense than normal, and more or less shrunken.

Microscopically, in the acute stage the ganglion cells present the usual changes under such circumstances—namely, they swell, the chromophilic substance undergoes a granular change or the masses run together, the nuclei become eccentric, and the cells ultimately disintegrate. The axis-cylinders passing from such nerve cells degenerate throughout their entire extent, as do also their myelin sheaths. As a consequence, the muscle-fibers to which they are supplied undergo fatty changes, and to a great

extent atrophy and disappear. This change in the muscles is the most striking clinical phenomenon, and as the disease generally occurs in infants, it has been long known as **infantile paralysis.** The glia cells swell and proliferate, and the tissues are infiltrated to a certain extent by small mononuclear cells. The blood-vessels that penetrate the affected region are distended; their walls not infrequently rupture, and more or less blood is consequently infiltrated into the part. If the inflammatory phenomena be severe, and if they persist for some time, the central area of the diseased region will be found to contain only the granular debris resulting from degeneration of all of the elements that go to make it up.

After the acute stages have passed the neuroglia proliferates and gradually replaces the degenerated tissue.

An interesting fact connected with this disease is that the motor cortex of the brain, in connection with the diseased parts, appears in the course of time to undergo more or less atrophy; this is probably the result of disuse.

Progressive Spinal Muscular Atrophy.—Closely related to acute anterior poliomyelitis in the seat of its spinal lesions is the disease known as progressive spinal muscular atrophy. It is not, however, at all certain whether the changes in the gray matter of the cord are to be regarded as of an inflammatory or of a degenerative kind, and it would therefore be obviously incorrect at the present time to class them with the inflammations; notwithstanding the uncertainty that still exists respecting its character, the disease is sometimes called **chronic poliomyelitis.** In this connection attention should be directed to the fact that injury, overwork, exposure to cold, or an attack of any of the infectious diseases are regarded as the most usual causes of this affection; as these are precisely the etiologic factors generally looked upon as being most potent in the production of ordinary myelitis, and as the lesion of progressive muscular atrophy could be very well the result of an inflammatory condition, it certainly requires no very great stretch of the imagination to conceive a closer relation between the two than is generally supposed.

Morbid Anatomy.—The gross changes in the cord are never very marked, but in the later stages sclerosis may be apparent in the anterolateral columns. The anterior nerve-roots are also much more dense than normal, owing to a great increase in the fibrous tissue between the nerve-fibers.

Microscopically, the ganglion cells of the anterior cornua, especially in the cervical region, gradually undergo degenerative change, and finally disappear. This is, of course, followed by degenerative changes in the nerves of the anterolateral columns,

and, later, by the development of a sclerotic condition as the result of the increase of neuroglia in the part. The changes in the nerves are in every way similar to the alterations following myelitis. It may be observed, however, that there is no evidence at any time of an inflammatory state in the gray matter, if the atrophy of the nerve cells be excepted. The motor nerve-roots show degenerative changes resembling those found in the cord, and the peripheral nerves exhibit the same alterations.

The muscles to which the affected nerves are supplied lose their striation, become granular, degenerate, and ultimately disappear; fat often takes their place.

Progressive Bulbar Paralysis (Glossolabiolaryngeal Paralysis).—Very closely related to progressive muscular atrophy is the disease of the medulla known as progressive bulbar paralysis. It occurs under exactly the same circumstances as does progressive spinal muscular atrophy, and even passes into it by gradual stages, or vice versâ. In fact, the only difference between the two seems to be the mere accident of location, one affecting principally the cervical region of the spine, and the other the medulla, which is but the cord continued into the skull. With the exception of the difference in location, the two diseases have exactly the same gross and microscopic anatomy.

Insular Scleroses of the Cord.—In discussing insular sclerosis of the brain mention was made of the fact that here and there small areas in the cord were also affected, and it will, therefore, not be necessary again to refer to this peculiar form of the disease.

Posterior Spinal Sclerosis (Locomotor Ataxia).—Of the scleroses of the cord the most common and typical is that variety called posterior spinal sclerosis. The disease seems in a large percentage of cases to be due to syphilis; it is also probable that alcoholic excesses, exposure to cold, overexertion, and injuries are responsible for a certain number of cases.

Morbid Anatomy.—On removal the cord generally presents, in advanced cases, a striking diminution in its anteroposterior diameter, owing to the fact that the sclerosed tissue that has taken the place of the nerve-fibers occupies less space than the normal nerve substance. The newly formed tissue is also of a darker color than the neighboring normal parts, and on section its consistence is found to be increased. The disease, as a rule, first appears in the lumbar region, and is most intense in this situation; however, the entire posterior columns of the cord may be involved in severe cases. The posterior nerve-roots may also show marked sclerotic change.

Microscopic examination shows that the
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is a dense network of neuroglia fibers.
fatty particles may be seen occupying the
In the later stages corpora amylacea are
upper portion of the cord the substance of th
umns is not affected, the disease here being
terior median column. Even in the lower p
of the nerves always escape; a small band

Fig. 338.—Spinal Cord, Showing Posterior
Tissue was hard ened by Müller's solution; sections stained in
Normal nerve fibers. A, Sclerotic area. (Queen o

the pia, and on each side of the posterior
median septum, are usually intact, as are als
anterior part of the posterolateral column
severe and of long standing, more or less
served throughout the entire cord. For a n
tion of the minute changes in the sclerosis
occurring in this disease the reader is re
on Insular Sclerosis of the Brain, page 77

is not greatly affected in posterior spinal sclerosis, but degenerative changes occur in the ganglion cells of the posterior cornua and in the nerve-fibers of the gray matter, especially those surrounding the vesicular columns of Clarke. The ganglion cells in the spinal root ganglia also degenerate, and the sensory nerves of the periphery show similar alterations.

From what has been said it will be seen that the disease does not affect the motor nerves, and, although incoordination in movement is a symptom of the malady, the muscles are not affected. The incoordination is entirely the result of a failure of the sensory nerve to convey the usual impulses to the sensorium, and a consequent vacillation on the part of the nerve center, from a lack of knowledge as to the relation of the body to surrounding objects.

Hereditary Ataxia (Friedreich's Ataxia).—As this affection is of a hereditary nature, it seems highly probable that its cause lies in some error of development.

Morbid Anatomy.—In this disease sclerosis of the posterior columns is invariably present, and, in the main, the lesion is similar to that of the ordinary form of posterior spinal sclerosis. The posterior nerve-roots are also affected. In addition to the sclerosis of the posterior columns, marked sclerotic changes in the lateral and anterior columns occur; the resulting involvement of the pyramidal tracts causes atrophy of the muscles that are innervated by the diseased nerves. The microscopic changes are the same as in the other scleroses.

Primary lateral sclerosis (primary spastic paraplegia) seems to be produced by the same causes that give rise to progressive muscular atrophy.

Morbid Anatomy.—The affection is characterized by a sclerosis of the pyramidal tracts, both lateral and anterior. The cord presents the macroscopic and microscopic appearances characteristic of all the sclerotic conditions, and as these peculiarities have been described in connection with the other forms of the disease, it would be useless to repeat them here.

This sclerotic condition is probably in all instances associated with, and really produced by, atrophic changes in the ganglion cells from which the nerves spring. In most instances in which accurate studies of the cord have been made marked alterations in the motor ganglion cells of the cord have been observed; the condition is, it will then be seen, very closely related to progressive muscular atrophy, and the opinion is gaining ground that the two conditions are really but varieties of the same disease. In some instances the sclerosed pyramidal tracts have

been traced through the brain to the mot
cells of which were found atrophied; in the
was probably due to the lesions in the nerve

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Morbid Anatomy.—The cord presents tl
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of the cord. They present the same gross
pearances that characterize growths of lik
The effects produced depend, of course, on
of the tumor. *Gliosarcomata* also occur. S
ties of *sarcomata* are occasionally seen. Se
and *sarcomata* are sometimes found. *Tub
gummata* may occur, but are quite rare.
echinococcus and *cysticercus* have been obser

THE NERVES.*

Nothing is known of the minor *circul*
nerves. It is probable that the quantity of
influenced in a greater or less degree by
produce like results in the central nervous s
of blood would certainly be increased in th
flammation.

Inflammation of Nerves (Neuritis).—
acute or *chronic*, and it may be limited to a
or the greater number of the nerves of
affected.

Etiology.—Injury of any kind is a frequer
neuritis. Inflammatory conditions in the
may give rise to it by a process of extension
seems to act in a causative way in some ins
eral diseases are also capable of setting up a

* For histology see p. 748.

probably as a result of the presence in the blood of toxic substances, which may be either the cause or the result of the initial pathologic process. Among such diseases are gout, rheumatism, diphtheria, the exanthematous diseases, typhoid fever, malaria, tuberculosis, septicemia, diabetes, syphilis, and leprosy. The disease occasionally occurs in the aged; this is probably often due to atheroma, or other disease, of the

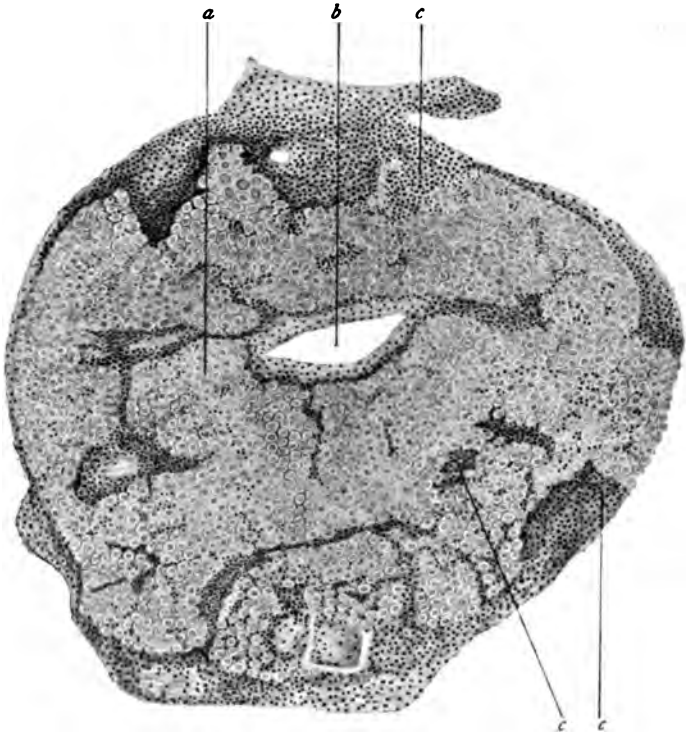


FIG. 329.—NERVE. ACUTE INTERSTITIAL NEURITIS.
Fixed in Heidenhain's solution; stained with toluidin-blue and eosin. *a*. Normal nerve-fibers. *b*. Blood-vessels. *c*, *c*, *c*. Collections of lymphoid cells. (Queen obj., ⅔-in.; oc. B.)

blood-vessels. There are a number of chemic substances, such as lead, alcohol, arsenic, silver, etc., that may also act as causative agents in the production of the disease. Lastly, there is an endemic form of multiple neuritis, known as *beriberi*, or *kakke*, that occurs principally in China and Japan, and is believed to be due to a special bacterial infection. In addition to beriberi, the most common form of multiple neuritis is that caused by

alcohol; the condition may, however, be t
other than alcohol and of any of the infecti

Morbid Anatomy.—On examination an ir
cially if the process be acute and of a decid
found to present a more or less reddened
be swollen. At a latter stage the nerve ma
extent, owing to the formation of fibrous tis
examination the nerve presents changes the
which depends upon whether the fibers or
be most affected; the former variety is c
neuritis; the latter, *interstitial neuritis.* In
interstitial changes are usually pronounced,
forms the myelin and axis-cylinder are
Either variety, if pronounced, ultimately gi

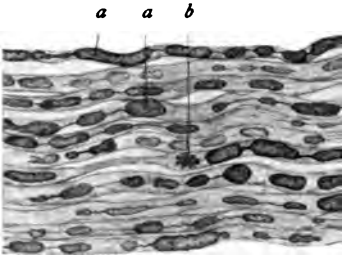


FIG. 330.—LONGITUDINAL SECTION OF MUSCULO-SPIRAL NER
WHO DIED AS A RESULT OF ALCOHOLIC MULT
Section hardened in Müller's solution; stained by Weigert's ne
Showing remains of myelin sheaths of nerves. *b.* Compoun
obj., ¼-in.; oc. B.)

In the acute stages the interstitial form s
croscope fullness of the blood-vessels, more
the tissue, and the accumulation of cells in
are multinuclear leukocytes if the process
lymphoid if otherwise. Slight extravasa
occur. These changes are usually localized
the track affected, though they may be dif
degree of uniformity. If the inflammation
fibers begin to show changes, which, whet
degenerative, it is difficult to say; the latter
correct one. The alteration first observed
the myelin into irregular masses that may
nected with one another by thin filaments of
If prepared by Marchi's method (p. 761),
show areas of fatty change. The axis-cy

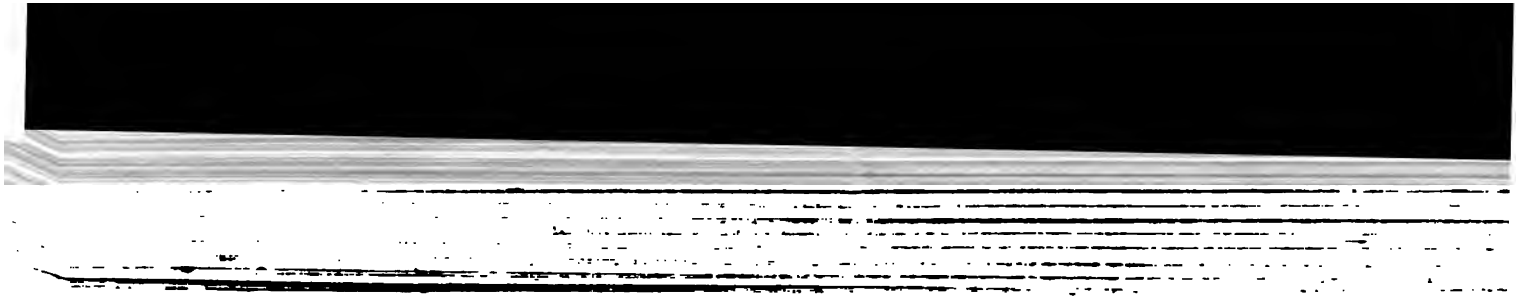
interrupted at the points where the myelin is divided. The nuclei of the nerve sheath increase in number. Gradually, the myelin further degenerates, and, in many parts of the nerve-fibers, entirely disappears; when this occurs, the primitive sheath collapses, and ultimately the entire nerve may be destroyed, being replaced by fibrous tissue. Compound granule cells make their appearance within and around the nerves as the process becomes older. If the inflammatory phenomena be slight, the nerve-fibers do not suffer to so great a degree. In the chronic forms the fibrous tissue may greatly increase in amount.

Whether the neuritis be primary or secondary the same alterations occur within the nerve-fibers involved. Degenerative changes occur in the muscle-fibers that are supplied by the diseased nerves. The fibers lose their striation, become granular, and their nuclei increase in number; they undergo atrophic changes in the affected region.

Degenerative changes in the nerve-trunk follow various spinal and many cerebral lesions. These changes differ in no way from those described in connection with what is called inflammation. The interstitial changes are, of course, but slight in these cases.

Regeneration of Nerves.—After the nerve is destroyed in one place the distal portion undergoes degenerative changes throughout its entire extent, while the proximal part degenerates upward to the first or second node of Ranvier. From this point *regeneration* occurs by the axis-cylinder growing downward, and usually dividing into three, four, or five separate fibers, each of which in a short time is enveloped by a distinct myelin sheath. These nerves grow downward within the primitive sheath of the degenerated nerve and follow it to its termination; just how the fibers become united with the end-organs is not known.

Tumors of Nerves.—Tumors of nerves are sometimes encountered. *Fibromata* are perhaps most frequent. They may develop anywhere along the course of the nerves. If they contain nerve-fibers, they are called *neurofibromata*. These tumors are usually multiple. Sometimes they form irregular, convoluted plexuses, containing thickened nerves; such new formations are then called *plexiform neuromata*. *Sarcomata*, *lipomata*, and *myxomata* occasionally occur. They are rare. They do not differ from similar tumors found elsewhere in the body.



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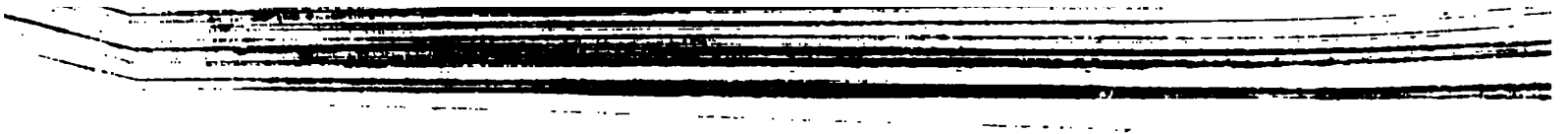

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